THE RÔLE OF INTRATHORACIC RECEPTORS IN THE CONTROL OF URINE FLOW.

Thesis presented for the degree of

DOCTOR OF MEDICINE

in

THE UNIVERSITY OF EDINBURGH

by

John Russell Ledsome, M.B., Ch.B., (Edinburgh).

Department of Physiology,
School of Medicine,
University of Leeds.

January 1962.

"Sir, I have found you an argument but I am not obliged to find you an understanding". Dr.Samuel Johnson, Boswell's Life of Johnson, June 1784.

CONTENTS.

INTRODUCTION.

The conception that the renal excretion of water and electrolytes is partly governed by the volume in some fluid compartment of the body is one which has recently attracted many investigators. The possible existence of a mechanism sensitive to changes in the "fulness of the blood stream", by which such a control could be exerted, was suggested by Peters (1935). Support has been provided by a theory that stimulation of sensory nerve endings in the intrathoracic circulation sets up afferent impulses in the vagus nerves which diminish the release of antidiuretic hormone from the neurohypophysis, and so causes diuresis. This theory has been developed particularly by Gauer and his co-workers (summarized by Gauer, Henry & Sieker, 1961).

It will be shown that sensory receptors exist in several sites in the intrathoracic vascular system and that their impulse discharge may be affected by changes in intrathoracic blood volume and by respiratory movements. Measures which lead to an expansion of the intrathoracic circulation are often accompanied by a diuresis, while depletion of this area is accompanied by oliguria. However, changes also occur in other parts of the circulation and these changes will be considered and an attempt made to assess the possible mechanisms involved in the production of the changes in urine flow. In particular, previous work often quoted as providing support for the theory that stimulation of intrathoracic receptors causes changes in urine flow will be reviewed.

A series of experiments has been carried out in an attempt

to define more closely either an afferent or efferent mechanism which would provide evidence of a link between intrathoracic receptors and urine flow. The results of these experiments will be discussed and it is believed that they allow certain conclusions to be reached regarding the theory that intrathoracic receptors influence urine flow. Some of these results have recently been reported in a condensed form (Ledsome, Linden & O'Connor, 1961).

PART I.

HISTORICAL REVIEW.

CHAPTER I.

SENSORY NERVE ENDINGS AFFECTED BY CHANGES IN INTRATHORACIC BLOOD VOLUME.

A. SENSORY NERVE ENDINGS IN THE HEART.

ANATOMY.

The first histological evidence of sensory nerve endings existing in the heart was presented by Berkley (1894) who had observed nerve fibres with swellings on their endings. Shortly afterwards Smirnow (1895) described complicated sensory endings in the atrial endocardium of mammals and amphibia. These endings showed extensive arborisation, the fine branches of which were associated with swellings. He also described a fine network in the endocardium which had varicosities along its length.

The sensory endings in the dog's heart were examined by Woollard (1926) who found both the muscular and non-muscular tissues were richly innervated. Medullated nerve fibres were found along the ascending aorta and in the wall of the 'auricle' adjacent to the aorta. The fibres ran in the adventitia but as they approached their termination they turned sharply inwards to end in the advential sheet superficial to the middle coat of the artery. In the 'auricle' they behaved in a similar fashion ending beneath the epicardium. As the nerve approached its ending it lost its medullary sheath and divided into an extensively branched end structure. In addition there were fine nerve plexuses in the subpericardial and endocardial tissues which were presumed to be derived from vagus endings. Woollard (1926)

reviewed the previous descriptions of sensory endings in the heart and considered his findings to be in agreement with earlier studies although Smirnow (1895) had described end structures in the subendocardium whereas Woollard (1926) only described these endings in the epicardium.

Nettleship (1936) made a study of the afferent innervation of the cat's heart and observed the effects of degeneration after section of the vagi and removal of the cervical sympathetic and stellate ganglia. He found a network of sensory fibres ramifying beneath the epicardium of both 'auricles' and ventricles, many fibres of which penetrated the myocardium to lie beneath the endocardium. An endocardial plexus also extended throughout the 'auricles' and ventricles, and was composed of non-myelinated fibres, although he considered it originated from larger myelinated fibres. Similar plexuses were observed in the adventitia at the base of the pulmonary artery and aorta. Sensory endings were described as arising from the subendocardial plexus, and were most numerous around the valves and at the base of the atrio-ventricular septum. Although the endings usually showed extensive arborization, variations from the simplest dot-like expansion up to a tree like form were seen. The nerve plexus and the specialized nerve endings degenerated when the vagus nerves were cut, but remained intact when only the motor elements of the vagus were destroyed.

Specific receptor areas were mapped out by Nonidez (1937) in the intrapericardial portions of the venae cavae and pulmonary veins. Using young rabbits, cats and dogs he found

that the muscular structure of the vessel walls in these areas resembled myocardium rather than that of veins, the transition in structure occurring just outside the pericardial reflexion. Plexuses were found in these areas similar to those described by Woollard (1926) in the outer coat of the wall. Nonidez (1937) claimed that his staining method using silver nitrate impregnation in contrast with the methylene blue used by other investigators gave some degree of specificity in staining sensory or afferent fibres. He criticized the use of section and degeneration as a means of identifying afferent fibres since such a procedure would also result in the degeneration of preganglionic efferents. Two types of nerve ending were found in the region examined. Large or medium sized fibres gave rise to subendothelial arborizations with their branches lying parallel to the endothelium and with reticulated swellings on the branches, these endings varied greatly in size and in degree of arborization. A second type of ending was found closely associated with the cardiac muscle fibres in the walls of the pulmonary veins in the kitten. Nonidez (1941) later described a more complicated type of ending in the dog, existing only in the area of transition between the pulmonary veins and left atrium and occupying the whole thickness of the subendothelial layer; these endings were more compact than those previously described which arborized parallel to the endocardial surface. The perimuscular endings were not found in the dog. After cervical and upper thoracic sympathectomy in the cat the endings in the superior and inferior vena cava persisted but the subendothelial and perimuscular endings in the pulmonary veins degenerated. However the presence of vago-sympathetic connections does not

allow any conclusions as to the course followed by the fibres in the pulmonary veins.

Using a similar staining technique Pannier (1940) confirmed Nonidez's findings in the adult cat. He described perimuscular endings in the wall of the intrapericardial part of the superior vena cava in addition to those found by Nonidez in the pulmonary veins. Similar endings were found in the myocardium of the right atrium and auricles. Elftman (1943) also described endings in the myocardium and endothelium of the terminations of the pulmonary veins and noted that such endings were lacking in sections further into the lung. She confirmed Nonidez's (1939) observation, that with this technique which failed to stain sympathetic postganglionic fibres, the small vessels in the lungs showed almost no innervation.

King (1939) claimed to have found endings in the ventricular myocardium resembling the muscle spindles found in striated muscles but of a simpler type. These endings had no capsule and appeared as branched nerve endings in close contact with the muscle fibres. He also observed encapsulated cylindrical whorls lying between parallel muscle fibres. However, other authors have denied the existence of specific end structures in the ventricles (Nonidez, 1943). Nonidez (1943) described very similar endings in the atria, presumed to be efferent endings, in which contact with muscle fibres is effected by means of terminal and subterminal rings, minute club-shaped dilatations and reticulated swellings. Tcheng (1951) claims to have found sensory endings in considerable numbers in the depths of the myocardium as well as in the subendocardial connective tissue. He observed both the arborizing

type of ending and also one which appeared as a series of granules united by fine filaments. In puppies and cats he found more sensory fibres in the right atrium than the left and rarely found them in the ventricles. He did observe a few endings in the ventricles one of which ended close to a blood vessel and he expressed doubt as to the significance of such endings.

In a general study of autonomic innervation Meyling (1953) found in all tissues investigated, including the heart, a network of autonomic interstitial cells representing the extreme peripheral part of the autonomic system. He claimed that the end ramifications of the afferent and postganglionic fibres were connected to this network by synapses. This nervous network along with the myocardial muscular network was pictured as a single functional neuromuscular tissue. This author considered the free nerve endings described by others as artefacts due to incomplete staining; even in areas such as the depressor zone of the aorta large myelinated afferent fibres were described as having their end branches connected with the terminal network. Mitchell (1956) also thought that many of the more complicated types of sensory ending described by previous workers might be kinked nerve fibres or bundles cut obliquely and really a part of the terminal network. He found terminal nerve networks in the subepicardium, myocardium and subendocardium of both atria and ventricles of the monkey. The fibres of these networks were non-myelinated but may have been derived from myelinated fibres which lost their myelin sheaths as they approached their terminations.

Large myelinated fibres were described by Sato (1954) in the dog atria but these were said to end freely in the endocardium or myocardium. Endings in the myocardium were usually unbranched whilst those in the endocardium showed a more complicated arborization. He also found a plexus between the epicardium and myocardium from which small branches ran into the myocardium.

Coleridge, Hemingway, Holmes & Linden (1957) by recording impulses from slips of the vagus nerves in the neck and then probing the atria were able accurately to localize the site of origin of the impulses. Histological studies of areas of origin were made using both silver impregnation and methylene blue stains. In every specimen in which functional localization of a receptor area had been achieved, one or more branched nerve endings were found. These arose from thick myelinated fibres running parallel to the endocardial surface and which were occasionally seen passing from the muscle to the endocardium. The end formations consisted of a branching of the thick fibres within a circumscribed area the myelin sheath being lost beyond the point at which branching occurred; the fine branching fibres and terminal filaments were closely associated with deeply impregnated cellular elements. In addition to these end formations there was a subendothelial nerve network formed of a typical pattern of branching fibres and interstitial cells. These two distinct structures were seen in both the silver and methylene blue preparations. The terminal nerve network whilst most prominent on the posterior atrial walls extended towards the atrio-ventricular orifices, into the veins and the atrial appendages, and onto the

anterior atrial wall. The thick fibres with their endings were limited to the atrio-venous junctional regions, to the proximal parts of the veins and the adjacent parts of the atrial wall and inter-atrial septum. Serial sections showed that these structures were not obliquely cut nerve bundles and it was possible to follow the fibres branching and ending in specific end structures, usually without connection with the terminal nervous network. Occasionally fine branches from the thick fibres or endings appeared to join the nerve net and the possibility of communication between the two structures could not be entirely discounted.

ELECTROPHYSIOLOGY.

Impulse activity in vagal fibres whose endings lay in the great veins and atria was first demonstrated by Amann & Schaefer (1943). Their records show discharges occurring during both atrial and ventricular systole and also some fibres showing activity during diastole. Walsh & Whitteridge (1944) observed fibres which showed groups of impulses corresponding to the 'a', 'c' and 'v' waves of the venous pulse and whose discharge varied with the effective venous pressure. Activity in these fibres increased with inspiration, decreased during expiration and was abolished by positive pressure inflation of the lungs. Similar fibres were described in more detail by Walsh (1947). Vagal fibres whose activity showed a cardiac rhythm were examined by Whitteridge (1948) using cats with the chest closed. He was able to show general agreement between effective venous pressure and the pattern of impulses in venous fibres. As previously

described, volleys of impulses corresponded to the 'a', 'c' and 'v' waves of the venous pressure pulse. Activity in these fibres was increased by normal or obstructed inspiration and also by compression of the abdomen. The 'v' volleys usually showed greater changes with respiration than the 'a' volleys. The impulses in these fibres were blocked by cooling to 8 - 12°C. Two fibres were observed whose activity decreased at the beginning of normal inspiration and increased sharply at the onset of expiration; these fibres probably arose from the pulmonary veins or left atrium. Another group of fibres was characterized by a late systolic volley of impulses which increased during inspiration and also when an intravenous infusion was made but decreased when the lungs were artificially inflated. The impulses in these fibres were not blocked by cooling until a temperature of 3-4°C was reached. It was suggested that these fibres might signal distending pressure in the arterioles or capillaries of the lungs.

Jarisch & Zotterman (1948) using open-chested cats were able to record activity from the nerve branches of the vagus running towards the atria. Their records showed volleys of impulses synchronous with the P wave of the electrocardiogram and a second late systolic volley reaching its maximum frequency at the end of ventricular systole. The second volley varied in frequency and duration and sometimes continued until the next auricular volley. Similar records were obtained from fibres from either the right orleft atrium but the second volley in these fibres from the left atrium was even more variable in both frequency and duration than fibres from the right atrium. Clamping the caval veins reduced

activity especially of the late systolic volley, clamping the pulmonary artery increased the discharge in fibres from the right atrium and decreased discharge from the left; when the aorta was clamped there was an increase in activity on both sides. Rapid injection of Ringer's solution increased the discharge and the injection of veratrine also caused a massive discharge. The site of the receptors was localized by probing the inside of the atrium and they were convinced that the receptors were situated around the orifices of the caval veins and also in the inter-atrial septum but not in the ventricles. The receptors were said to be stimulated by atrial distension and by the mechanical events of the heart. Besides large spikes from receptors in the atria many small spikes were seen, which were said to be produced by very thin nerve fibres. These were also stimulated by clamping the pulmonary artery or aorta, and by veratrine, and slowly conducted volleys were seen when the ventricles were pinched.

Dickinson (1950) showed that the frequency of discharge in the fibres from the right atrium was related to venous pressure. In addition to a volley of impulses coincident with atrial systole he also described volleys occurring in late ventricular systole similar to the discharge from arterial pressoreceptors. Fibres similar to these which showed impulse activity in late systole were examined by Pearce & Whitteridge (1951) who worked on cats and other mammals breathing spontaneously. The discharge in these fibres increased during inspiration and decreased during

the expiratory pause. Positive pressure inflation of the lungs stopped the discharge whilst negative pressure deflation caused an increase in both frequency and duration of discharge. The authors considered that the receptors for these fibres lay in the pulmonary vascular bed and related the discharge to variations in pulmonary arterial pressure. Changes in pulmonary artery pressure produced by respiratory manoeuvres corresponded closely with the fibre impulse activity, although there was a time lag between the peak pressure in the pulmonary artery and the peak discharge frequency. This lag was accounted for by a calculation of the time taken for the pulse wave to reach the pulmonary arterioles. These supposedly pulmonary vascular receptors were reinvestigated by Paintal (1953a) who used open chested cats. Fibres were first identified with the chest closed on the criteria laid down by Whitteridge (1948).

1. A late systolic discharge with no impulse activity accompanying the 'a' wave of atrial pressure.
2. Activity increased by an increased venous return produced by normal or obstructed inspiration or by suction of air from the trachea.
3. Activity decreased or abolished during positive pressure inflation of the lungs.

When a fibre showing these characteristics had been identified the chest was opened and the receptor localized by occluding the pulmonary artery and atrio-ventricular junctions. Ten fibres were examined in this way; of these six showed an increased discharge when the pulmonary artery was was occluded and also when

the right atrio-ventricular junction was occluded; whereas in four the activity decreased when the pulmonary artery was occluded but increased when the left atrio-ventricular junction was occluded. The endings of these fibres lay in the right and left atria respectively. Their presence in the atria was confirmed by making a water-tight chamber of each atrium and filling it with saline, an increase in the volume of fluid in the chamber increased the receptor discharge. The effective stimulus to these receptors was therefore a stretch of the atrial wall and their normal discharge in time with the 'v' wave of the atrial pressure is at a time when the atrium is at its maximum volume. Paintal (1953a) called these 'Type-B receptors' to distinguish them from those whose activity coincided with the atrial 'a' wave which he called 'Type-A receptors'. The behaviour of the receptors on the right and left sides was similar although there were some differences in the timing of the peak discharge during respiration. As Paintal (1953a) noted, these can be accounted for by the changes in size of the right and left atria during the respiratory cycle described by Cahoon, Michael & Johnson (1941).

Although Paintal (1953a) laid down strict criteria for the recognition of Type-B receptors his records do show that there may be considerable variation in the timing of the discharge from the receptors. For instance in Fig.1 of his paper the discharge does not begin until after the T-wave of the electrocardiogram and must be regarded as diastolic rather than late systolic. As a result of his experiments with the isolated atrium he concluded that the type-B atrial receptors do not respond to intra-atrial pressure

changes but are stretch receptors responding to change in atrial filling. But these receptors do not respond only to atrial filling as is shown by Fig.8A of his paper which plots increases in frequency of discharge of left atrial type-B fibres occurring in response to spontaneous contractions of a distended isolated left atrium. The increased discharge at this time cannot be due to an increased volume but must be associated with a change of tension in the atrial wall. Paintal suggests that this discharge does not occur in the normal heart because the atrial volume would be reduced by emptying of the atria at this time. However it is obvious these receptors respond to distortion which may result either from atrial filling or contraction of the atrial muscle. The discharge during atrial systole would then depend upon the position of the receptor in the atrium and on the force and direction of spread of contraction over the atrial wall and Paintal (1953a) did find that type-B receptors sometimes showed an 'a' volley when the chest was opened; this was attributed to a change in position of the heart.

Henry & Pearce (1956) examined similar afferent vagal fibres in the dog. All the fibres they examined arose from the left atrium and obstruction of the mitral orifice by distension of a balloon in the left atrium caused a marked increase in impulse activity. Pulmonary vein ligation usually caused a decrease in activity whilst negative pressure ventilation caused a small (15%) increase in activity. Intravenous infusions caused a rather greater increase in activity whilst haemorrhage was associated with a decrease. They found that impulses in

these fibres were blocked by cooling to between 4.5 - 12°C. They considered that these findings and the absence of discharge in the fibres during atrial systole supported the view that these receptors responded to stretch or atrial filling rather than to atrial pressure. They found a 30-40% haemorrhage and the intravenous injection of 100 µg of adrenaline altered the diastolic discharge to a high frequency early systolic one (Pearce & Henry, 1955); in these circumstances a decrease in atrial volume is to be expected and they suggested that the change was the result of mechanical effects on the atrium.

Whitteridge (1955) suggested that the type-A receptors behaved as though the endings were in the great veins in series with the contractile elements whilst the type-B receptors behaved as though they were in parallel with the contractile elements. The type-A receptors would then signal pressure and the type-B distension.

Coleridge, Hemingway, Holmes & Linden (1957) recorded impulses from atrial receptors in open chested dogs. In these experiments there was not always the expected change in impulse activity from these receptors with respiratory manoeuvres and the authors were doubtful whether the classification of atrial receptors into two distinct functional groups, one responding to pressure the other to alterations in length could be applied at least to their results obtained in open chested dogs.

Changes in impulse frequency in atrial receptors have been found to parallel changes in effective atrial pressure during respiration (Coleridge & Linden, 1959). The frequency of the

discharge at the 'v' wave from type-B receptors in the right atrium increased with the first cardiac cycle of a normal inspiration, the frequency reached a peak at the height of inspiration and decreased immediately with expiration. With receptors in the left atrium the frequency of discharge did not increase in the first cardiac cycle of inspiration but usually in the second or third cycle and this increase was sometimes preceded by a decrease in the frequency of discharge. The maximum rate of discharge occurred approximately with expiration. Coleridge & Linden (1959) found the changes in effective pressure at the corresponding point in the pressure wave of the appropriate atrium to follow a similar time course.

Chapman & Pearce (1959) have recorded impulses in fibres from the vagus nerve of the monkey which show activity similar to that seen in fibres arising from the atria in other animals.

Recently Langrehr (1960, a & b) has described four groups of impulse activity arising from atrial receptors in dogs and cats. In addition to the A & B type volleys described by Paintal (1953a) in atrial systole and late ventricular systole he described an 'E' volley in early systole, previously found in a few fibres by Paintal (1955) and a 'D' volley occurring during diastole especially at slow heart rates when filling was prolonged. Although some fibres showed only the activity characteristics of the type-A and type-B fibres, many fibres showed in addition volleys of impulses in early systole and diastole and the type of activity in any one fibre changed sometimes spontaneously and on other occasions following injections

of adrenaline. He found that frequency of impulses in the 'B' volley was best correlated with the strength of the heart beat whilst the frequency of impulses in the 'D' volleys depended on the rate of rise of pressure in the atrium during diastolic filling. Langrehr & Kramer (1960) studied more closely the impulse frequency from atrial receptors during infusion and haemorrhage of up to 25% of the blood volume and after injections of adrenaline and papaverine. They concluded that atrial receptor discharge was best related to intrathoracic blood volume but that the frequency of discharge depended not only upon this static relationship but also upon the dynamic state of the circulation.

There have been relatively few reports of impulses in afferent nerve fibres originating in the ventricles. Amann & Schaefer (1943) considered that at least some of the fibres they examined, which showed volleys of impulses during systole, originated in the ventricles. Jarisch & Zotterman (1948) did not observe any increase in the rate of discharge of large fibres when they handled the ventricles, but they did observe small slowly conducted spikes if the ventricles were pressed. Whitteridge (1948) described several fibres with early systolic discharge of impulses which began before the aortic valves opened and could not therefore have been aortic baro-receptors and Dickenson (1950) observed similar fibres. Paintal (1955) found eleven fibres in thirtysix cats in which he considered the receptor lay in the ventricles, seven of these were eventually localized to the right ventricle and the other four to the left.

They showed an early systolic burst of impulses within 20-30 m-sec of the Q wave of the electrocardiogram and therefore discharged during the phase of isovolumic contraction of the ventricles, but some were excited during the ejection phase when intraventricular pressure reached its peak. They showed an indefinite response to respiratory variations and were not affected by anoxia; although all the ventricular receptors were strongly stimulated by injection of veratridine the atrial receptors were not affected. This latter finding agrees with that of Dawes & Widdicombe (1953). Paintal (1955) does however claim that veriloid which also stimulated ventricular receptors stimulated about one-third of the left atrial receptors, but as the peak discharge occurred after bradycardia was produced it seems at least possible that this could be a secondary effect dependent upon haemodynamic changes. The conduction velocity in the ventricular fibres was between 10-20 m/sec and they were therefore said to belong to the A group of medullated nerve fibres.

Reflex bradycardia and hypotension induced by injection of veratridine into the left coronary artery was not abolished by division of the aortic depressor nerve, left recurrent laryngeal nerve and the left anterior cardiac nerves. Only when the left posterior cardiac nerves were cut was the effect abolished and to reach these the left pulmonary artery must be removed (Dawes 1953). These nerves run over the posterior surface of the left atrium and may join the recurrent laryngeal nerve as it crosses the aortic arch (Dawes & Widdicombe, 1953). Fibres from

receptors in the left atrium are often found in the main trunk of the left vagus nerve below the origins of the recurrent laryngeal nerve and the anterior and posterior cardiac nerves (Coleridge & Kidd, personal communication). Fibres from the right atrium may join the main trunk of the right vagus nerve at or below the level of the right atrium (Jones, 1953).

FIBRE SIZE.

Several investigators have estimated the size of the afferent nerve fibres connected with specific end-structures in the atria. Jarisch & Zotterman (1948) found that discharges from atrial receptors in the cat were carried in myelinated fibres with a diameter of 2.8 - 7 μ, whilst Whitteridge (1952) tentatively ascribed a diameter of 4 - 7 μ. Nettleship (1936) using degeneration showed that large endocardial fibres of 6 μ were probably afferent, and Daly & Evans (1953) studying degeneration after section of the vagus nerves at various levels concluded that afferent impulses from the heart travelled in myelinated fibres of 1 - 14 μ diameter with the majority of them 4 - 6 μ. Coleridge et al. (1957) estimated the fibres running into end formations in the endocardium had a diameter of 3 - 10 μ whilst the fibres of the terminal network were always smaller.

Paintal (1953b) studied the conduction velocities in respiratory and cardiac afferent fibres in the vagus nerves. Type A atrial receptor fibres had a mean conduction velocity of 20m/sec (range 13-27), type B from the right atrium 13m/sec

(range 8-23) and type B from the left atrium 20m/sec (range 15-26). Fibres carrying impulses from pulmonary stretch receptors had a mean conduction velocity of 36m/sec (range 14-59) and from aortic baroreceptors 33m/sec (range 12-53). The considerable overlap of conduction velocity in these fibres makes their identification by this means impossible and makes unlikely the possibility of blocking only one type of afferent fibre by cooling the vagal trunk.

B. SENSORY NERVE ENDINGS IN THE PULMONARY VASCULAR SYSTEM.

ANATOMY.

A rich nerve plexus in the wall of the pulmonary arteries and extending over the arterioles was described by Larsell (1921). The terminal fibres of this plexus entered the media and ended in close relation to the smooth muscle cells. Discrete sensory endings were found only in the walls of the pulmonary arteries close to the hilum of the lung. In contrast to the rich nerve plexus over the arteries the pulmonary veins were found to have few fibres (Larsell, 1922). The periarterial plexus was later described by Larsell & Dow (1933) as being composed of postganglionic fibres from the upper sympathetic ganglia. Arborizing sensory nerve endings showing terminal knobs were found in the adventitia of the pulmonary arteries near their bases and also in the secondary branches in the lungs. Takino (1933) and Takino & Watanabe (1937) also described sensory endings in the right and left branches of the pulmonary arteries extending

between the bifurcation and the lung roots; they were unable to find any endings in the main pulmonary trunk. The existence of specialized pressoreceptors in the wall of the pulmonary trunk and proximal portions of the pulmonary arteries was denied by Nonidez (1935) but he did find an accumulation of typical sensory nerve endings around the base of the ligamentum arteriosum (Nonidez, 1941). Pannier (1940) found nerve terminations which he thought were similar to those in the arch of the aorta near the bifurcation of the pulmonary artery, and in one kitten examined, in the wall of the right pulmonary artery. Boyd (1941) made a study of the ductus arteriosus in a variety of mammals of all ages. Whilst the ductus itself had a rich afferent nerve supply relatively few fibres were found in the walls of the pulmonary arterial trunk or its branches. Although occasional sensory nerve endings were found in these latter vessels they were never so richly branching as those found in the ductus arteriosus. The fibres passing into the wall of the ductus usually ended in the outer third of the media. Their endings were extensively branched and possessed small thickenings and rings similar to those found in other presso-receptor areas. The number of endings was greatest at the aortic end of the ductus. Bianconi & Green (1959b) described sensory nerve endings in the adventitia of the right pulmonary artery as having characteristic arborizations with swellings and enlargements on the terminal twigs. In an electrophysiological study in the dog Coleridge & Kidd (1960), after identifying fibres in the cervical vagus, were able by probing the pulmonary artery to localize the position of

the receptors. All the receptors localized in this way were situated near to the bifurcation and the origin of the lobar branches; no receptors were found in the main pulmonary trunk itself. More recently these observations have been extended (Coleridge, Kidd & Sharp, 1961) to include histological studies of receptor areas localized by electrophysiological methods. The position of 44 receptors was determined; 20 of these lay in the right pulmonary artery and 20 in the left pulmonary artery, of which 11 were situated near the attachment of the ligamentum arteriosum. The main pulmonary trunk was devoid of receptors. Attempts to localize receptors in the ductus arteriosus of very young animals were unsuccessful although there can be little doubt on the evidence already quoted that such endings exist. Specimens of the pulmonary arteries taken at random and others in which there was electrophysiological evidence for the presence of a baroreceptor were examined histologically. Myelinated nerve fibres were seen in the adventitia terminating at the junction of the media and adventitia or penetrating into the media and ending as an irregular collection of fine coiled fibres embedded in connective tissue. Many other nerve fibres in addition to those terminating as specialized receptors were observed. Bundles of non-myelinated fibres in the adventitia accompanied the vasa vasorum into the media, and small groups of ganglion cells lay within the bundles of non-myelinated fibres in the adventitia.

ELECTROPHYSIOLOGY.

The first electrophysiological evidence of the existence of pulmonary arterial baroreceptors was provided by Swan & Whitteridge (1956) who recorded impulses from a single receptor in the pulmonary artery of the cat. This finding was confirmed by Bianconi & Green (1959b) and shortly afterwards Coleridge & Kidd (1960) provided evidence of such receptors in the dog. Pulmonary arterial baroreceptors display a cardiac rhythm very similar to that of aortic baroreceptors in that the main discharge begins in ventricular systole soon after the opening of the pulmonary and aortic valves, as judged by the relation of the discharge to the QRS complex of the electrocardiogram. Discharge from these receptors is abolished by occluding the main pulmonary trunk and increased by occluding the lung roots. Some receptors localized to the pulmonary artery may show unexpected patterns of discharge, for example Coleridge & Kidd (1960) illustrated one fibre which showed impulses during atrial systole but after infusion of dextran its main activity was during ventricular systole. This receptor lay in the right branch of the pulmonary artery behind the superior vena cava. In general the discharge in the pulmonary arterial receptors was increased whenever pulmonary arterial pressure increased, but because the pattern of discharge may be affected also by the position of the receptor the authors emphasize that a receptor cannot be assigned with certainty to a particular great vessel or chamber of the heart by the timing of the discharge, it must be located by appropriate means in an animal with the

chest open. The discharge from the pulmonary arterial receptors is affected by pressures within the physiological range and pulsatile pressures provide a more effective stimulus than steady pressure (Coleridge & Kidd, 1961).

C. SENSORY NERVE ENDINGS IN THE AORTA.

ANATOMY.

Early studies by Smirnow (1895) described the endings of medullated nerve fibres in the heart and ascending aorta. In mouse and rabbit embryos the right depressor nerve supplies the area around the subclavia whilst the left depressor supplies the aorta and also spreads to the caudal surface of the 6th aortic (pulmonary) arch (Tello, 1924). These nerves show a rich terminal ramification surrounding the arch of the aorta. An adventitial nerve plexus at the base of the aorta and pulmonary artery was said by Nettleship (1936) to be continuous with the subepicardial plexus of the heart. Although the fibres of this plexus varied in size the endings were of a single complicated arborizing type with swellings on the terminal twigs. They lay in the extremely superficial layer of the connective tissue of the adventitia and in the outermost coat of the media, and were unaffected by stellate ganglionectomy.

A detailed study of the distribution of the aortic afferent fibres in the rabbit was made by Nonidez (1935). The right aortic nerve ended around the base of the subclavia with the majority of the terminations on the supero-posterior aspect of

the vessel; the left aortic nerve had a more extensive distribution over the supero-posterior aspect of the aorta forming a vertical crescent mesial to the origin of the left subclavia. This meant that the anterior surface of the aorta had few terminations whilst the caudal or concave portion of the arch was abundantly supplied. This area received a few nerve fibres directly from the left vagus and a few fibres of the anterior branch of the left aortic nerve extended onto the ductus arteriosus to end in simple arborizations. No afferent nerve endings were found in the aortic wall outside the area described. Nerve terminations were large and ranged from a diffuse complicated arborization to a compact ending but all characteristically had swellings and enlargements on the terminal twigs. The nerve fibres did not branch extensively before reaching their terminations and the type of ending was not related to fibre size. Most of the endings were in the externa between the externa and the media and a few endings lay in the outer half of the media. Nonidez (1935) suggested that the diversity of size and shape provided a histological basis for the possibility of variable frequencies of discharge and the existence of diverse thresholds of stimulation. In a later paper Nonidez (1941) found that although in the newborn puppy all the nerve endings had a relatively simple structure, the endings of thick fibres increased in complexity whilst those of the fine fibres remained simple. Both types of ending were found in the adventitia and outer third of the media and both

were found only in the area already described. The simple endings lacked the massive reticulated swellings found on the endings of the thicker fibres but Nonidez (1941) considered both types of ending to be pressoreceptors. The pressoreceptor area was well defined at birth and growth of the aorta did not result in any marked scattering of the pressoreceptors.

The number of myelinated fibres in the depressor nerve of the rabbit has been established as between 150 to 600 (O'Leary, Heinbecker & Bishop, 1934). This figure is similar to that found in the cat (Agostini, Chinnock, Daly & Murray, 1957) where a total of 450 fibres was found, two-thirds of which were myelinated. The latter authors estimated the size of the fibres as having a bimodal distribution with peak 2-4 μ and 8-10 μ, whilst O'Leary et al. found the size to be 2-5.5 μ with some larger fibres of 9-10 μ.

ELECTROPHYSIOLOGY.

Einthoven (1908) showed that there were changes in currents recorded from the peripheral portion of the divided vagus nerve of the dog, which occurred during inspiration and also observed a series of more rapid oscillations synchronous withthe heart beat. In the rabbit the respiratory and cardiac effects could be separated by leading off from either the vagus or the cardiac depressor nerve (Einthoven 1911). Adrian (1926) using a capillary electrometer in place of the string galvanometer was able to record changes in potential in the vagus nerves of cats and rabbits. Oscillations of the record occurred with respiration

and the frequency and amplitude of the oscillations was greatest at the height of inspiration; in the record from the cat there were also groups of oscillations in time with the heart beat. Records from the depressor nerve of the rabbit showed groups of oscillations synchronizing with the heart beat and with a distinct pause between the groups. With the evidence of Koster & Tschermak (1903) who showed a negative variation in the depressor nerve associated with distension of the aorta, Adrian (1926) concluded the outbursts of impulses to be due to the rise in pressure in the aorta during systole. He also noted a great increase in the oscillations when adrenaline was injected intravenously. Bronk (1931) was able to show that the large outburst of impulses in the depressor nerve was in fact synchronous with the rapid rise in pressure of the aorta. The activity of the nerve endings appeared to be a function of both the absolute level of pressure and the rate of change of pressure. These findings were confirmed by Rijlant (1932) and Adrian (1933). Single functional fibre preparations of the depressor nerve were examined by Whitteridge (1948) who noted that the peak frequency of discharge of the fibres was sometimes affected by changes in intrapleural pressure and also to some extent by mechanical changes at the root of the lung. The discharge from these receptors is characterized by an early systolic volley beginning 36-38m/sec after the Q wave of the electrocardiogram and reaching peak frequency between 53-106 m sec (Paintal, 1953b). During normal respiration maximal activity occurred at the beginning of expiration but positive pressure inflation of the

lungs reduced the activity of the systemic arterial receptors.

Marguth, Marguth & Raule (1951) classified the impulses in the aortic nerves of the cats and dogs into two types; those occurring synchronously with the pulse and those discharging continuously. The discharge occurring with the pulse was increased by a rise in pressure produced either by clamping the descending aorta or by injection of adrenaline or noradrenaline; the action of these drugs depended only upon their ability to raise the blood pressure. The activity of the continuously firing axons was augmented by asphyxiation, low blood pressure and noradrenaline and lowered by adrenaline; these were probably fibres arising from chemo-sensitive endings. These results differ from those found by Landgren, Neil & Zotterman (1952) in the carotid sinus; here application of adrenaline and noradrenaline to the sinus wall caused an increased discharge of baroreceptor fibres. However, Floyd & Neil (1952) were unable to show that stimulation of the sympathetic supply to the carotid sinus had any effect on impulse activity and concluded that sympathetic nervous activity was of little practical importance in modifying baroreceptor activity.

The comparative ease with which a perfusion preparation of the carotid sinus may be made has meant that the effects of applying a known stimulus to the baroreceptor endings have been studied in the carotid sinus rather than the aorta. However there is no doubt that the impulse frequency in aortic nerve fibres is reduced as mean arterial pressure is lowered (Neil,1954). The carotid sinus baroreceptors are more powerfully affected by

a pulsatile pressure than a steady pressure of the same mean value (Ead, Green & Neil, 1952) and it is likely that the aortic receptors are affected similarly.

D. PULMONARY STRETCH RECEPTORS.

ANATOMY.

Sensory nerve endings have been found widely distributed throughout the lungs. Larsell (1921) studied these nerve terminations in the rabbit and described the ramifications of large myelinated fibres in the bronchial walls especially in the epithelium at the point of division of the bronchi. These endings were found in all sizes of bronchi but in the larger branches the endings were more complicated and were sometimes found within a small epithelial swelling. The most distal point of the air passages at which he found sensory endings was just inside the atria. Larsell (1922) extended these observations and found in addition sensory endings in the smooth muscle of the bronchial walls. These endings arose from thick myelinated fibres and were composed of numerous short terminal branches some of which wrapped around the muscle whilst others ended between the muscle fibres; these endings were found wherever the smooth muscle existed. Examining the innervation of the human lung Larsell & Dow (1933) found nerve endings in the epithelium of the bronchi wherever the bronchi divided, similar to those previous described in the rabbit. These endings were present in the bronchial epithelium up to the base ofthe alveolar ducts and their ramifications with terminal twigs and knobs suggested they might be tactile receptors. Flattened

end-organs were found in the epithelium of the air sacs and the authors suggested that these were unlikely to be subjected to mechanical stimulation and might therefore be chemoreceptors. These were the most distal receptors found. Endings corresponding to those in the smooth muscle of the rabbit were found at various points in the smooth muscles of the bronchial wall. Coarse myelinated fibres ended in plate-like masses on the muscle. Elftman (1943) also described afferent endings in the smooth muscle of the respiratory tree. The epithelium of the lung was supplied with a variety of endings from the trachea to the walls of the alveoli in which in contrast to the previous investigators delicate straight or coiled terminations were found. She suggested that this large group of endings gave rise to pulmonary reflexes but found it impossible on histological grounds to determine the differential excitability of the various types of endings.

ELECTROPHYSIOLOGY.

As already described Einthoven (1908) and Adrian (1926) were able to show changes in electrical activity in the vagus nerves during respiration; the frequency and amplitude of the recorded oscillations was greatest at the height of inspiration. These findings were extended by Partridge (1933) who found the frequency of impulses in the vagus nerve of the rabbit varied directly with the volume of inspiration. No increase in discharge was found on inhalation of equal volumes of air and carbon dioxide. Adrian (1933) succeeded in obtaining records of single functional fibre preparations of the vagus nerve in cats, and described activity of various types.

Some fibres showed a pure cardiac rhythm, some a pure respiratory rhythm, while others showed discharge affected by both cardiac and respiratory events. The respiratory discharges showed an increase in the frequency of impulses rising to a maximum at inspiration and falling to a minimum as the lungs contracted. The discharge adapted only slowly to the stimulus. Adrian suggested that the stimulus was the actual deformation of the tissues in which the endings were placed. The pressure of the air in the lungs was immaterial as the discharge was the same for a given degree of expansion whether produced by positive or negative pressure inflation. In addition to fibres affected by inflation, forcible deflation by suction caused a discharge in other fibres and whilst he recognised the possibility that extreme deflation or inflation might stretch the tissues in which the endings responding to inflation lay, he had no doubt that deflation called a new set of endings into play as well. He supported this statement with the evidence that extreme deflation of the lungs caused an immediate inspiratory effort, whereas inflation of the lungs inhibited inspiration. However, he was doubtful of the part such endings might play in normal breathing as extreme deflation was necessary to produce the discharge. It is interesting that suction of air from the lungs (as in breathing from a reservoir at reduced pressure) did not necessarily have the same effects as increased pressure outside the thorax. Suction may stretch some of the endings which are normally stretched at inspiration but increased external pressure is unlikely to do so; increase of

external pressure reduced the afferent vagal discharge although it was accompanied by an increased respiratory rate this occurring most frequently when the resting rate of discharge during expiration was high. Partridge (1939) recorded impulses in few fibre preparations of the pulmonary branches of the vagus. These contained fibres stimulated by distension, by extreme artificial deflation and also some fibres with a cardiac rhythm which she regarded as afferent cardiac fibres. When the fibres were cooled to between 8-4°C impulses from stretch receptors were reduced but those showing cardiac rhythm remained.

The activity in fibres from stretch endings was found to be unaffected by pulmonary congestion in the perfused cat's lung (Bulbring & Whitteridge, 1945). They suggested that reflexes arising from other than stretch afferents in the vagus may be involved in the increased respiratory rate associated with pulmonary congestion. Walsh & Whitteridge (1944) were unable to find any effect on the sensitivity of the vagal stretch endings caused by injection of starch which causes multiple pulmonary emboli. They did however note an increased discharge from receptors presumably in the veins; the 'a' and 'v' wave discharge being greatly increased. Knowlton & Larabee (1946) describe two types of pulmonary stretch receptors according to the rate of adaptation of their end organ. They recorded the responses of single afferent fibres in the vagus nerves to changes in lung volume. Slowly adapting receptors had a lower inflation threshold than rapidly adapting receptors and whilst some receptors of both types responded to deflation some were

found which responded only to inflation. Conduction velocities were 8-44 m/sec. They suggest that impulses from slowly adapting receptors inhibit inspiration, whilst those from rapid adaptors excite it. Only the slowly adapting fibres would be active in eupnoea the threshold of the rapid adaption being above that usually attained. Widdicombe (1954a) investigated the activity of respiratory receptors during inflation of the lungs more thoroughly. He came to the conclusion that the receptors which gave the most rapid adaptation lay in the tracheobronchial tree and that their rapid adaptation was an artefact dependent upon the elastic properties of the lung parenchyma. Widdicombe listed three types of tracheo-bronchial mechano-receptors:

1. Rapidly adapting receptors in the tracheal epithelium sensitive to mechanical stimulation and responsible for the cough reflex.
2. Receptors with intermediate rate of adaptation in the epithelium of the trachea and bronchi and sensitive to both mechanical and chemical stimuli.
3. Slowly adapting bronchial receptors which resembled the deflation receptors of Adrian (1933) in their slow adaptation to deflation but were excited also by high thresholds of inflation. It is suggested that these receptors may lie in the smooth muscle of the bronchial walls.

In addition activity was recorded from receptors in the mediastinum whose discharge was also affected by inflation and deflation of the

lungs.

Widdicombe (1954b) made four further investigations to localise the site of the receptors responsible for the Hering-Breuer inflation reflex in the cat. The endings were not destroyed by removal of the visceral pleura but their discharge was affected by changes in bronchial tone. Broncho-constriction caused an increased discharge whilst broncho-dilation caused a decrease. He concluded that the majority of the pulmonary stretch receptors lie in the intrapulmonary bronchi and notes the great variation in response to deflation, cardiac modulation of rhythm and response to drugs when the receptors are studied by this method of recording activity in afferent nerve fibres.

Marshall & Widdicombe (1958) studied the activity of pulmonary stretch receptors during congestion of the lungs in cats with closed chests. A balloon was placed in the left atrium via the appendage and pulmonary congestion caused by inflation of the balloon so as to raise left atrial pressure by 20-40 cm H_2O. An increased discharge to a standard inflation by a pump or syringe was found when the lungs were congested; interpretation of effects during spontaneous respiration was difficult unless the tidal volume was unaltered. The sensitization of the end organs was presumed to be due to a greater stretching of the air passages when the compliance of the alveoli was reduced by congestion. Costantin (1959) investigated the same problem by isolating the lower lobe of

the left lung so that its artery and vein could be easily occluded. He also studied the effects of pulmonary congestion with air distension provided by means of a pump or by inflation with a syringe. He recorded action potentials in single functional fibre preparations of the cervical vagus and described two types of response to pulmonary congestion. In one group pulmonary congestion increased fibre activity throughout the respiratory cycle whilst in the other group activity was only increased at low lung volumes, that is during expiration. Occlusion of the pulmonary artery produced either an increase or decrease in activity. Some fibres showed a cardiac rhythm throughout the pulmonary cycle but occlusion of the pulmonary veins had no consistent effect on these fibres in some cases abolishing it whilst in others seeming to enhance it, such a cardiac rhythm might be due to movements of the mediastinum or conduction of ventricular systole from the heart, or great vessels, or to a vascular pulsation within the lung parenchyma itself. Evidence available suggests that such a cardiac rhythm depends upon distension of the pulmonary arterial tree itself.

Bianconi & Green (1959a) studied afferent discharge in those fibres showing both cardiac rhythm and an inspiratory discharge. Their findings show only that the timing of the cardiac discharge may vary in relation to the electrocardiogram and that this discharge may be affected by external mechanical factors such as the position of the chest or pressure on the thorax. There seems little reason for suggesting that these pulmonary stretch receptors showing a cardiac rhythm are in any way distinct

from those without a cardiac rhythm or that they represent an "Early signalling system of pulmonary congestion". Marshall & Widdicombe (1958) and Costantin (1959) stress the fact that any reflex effects of pulmonary congestion cannot be attributed only to an increased discharge in pulmonary stretch receptors.

Whilst these receptors constitute the majority of endings in the chest there is no doubt that sensory endings exist in other tissues in the chest and may be affected by cardiovascular or respiratory changes. For example Coleridge & Kidd (1960) describe a receptor situated in the connective tissue between the pulmonary artery and aorta and showing the characteristics of a pulmonary, or aortic baroreceptor. Holmes & Torrance (1959) investigating the afferent fibres of the stellate ganglion found receptors near the thoracic inlet stimulated by movement of the trachea. Other fibres came from receptors in the upper mediastinum, from the pleural folds near the lung roots and inflation of a balloon in the oesophagus stimulated receptors over or near to it. Such receptors were also affected by movements of the pulmonary artery and aorta.

SUMMARY.

Two types of nervous structures are regularly found in the heart, a network of fine non-myelinated nerve fibres and interstitial nerve cells exists throughout the endocardial, myocardial and epicardial layers, and secondly, arborizing nerve endings connected with myelinated fibres of about 3-10 μ in diameter exist in the subendocardium of certain areas of the atrial walls. These nerve endings are found only on the posterior atrial walls, in the junctional region between the venae cavae and pulmonary veins and the atria and occasionally on the interatrial septum. The adequate stimulus producing activity in the atrial receptors is distortion of the nerve endings. Some receptors discharge during atrial systole and may be stretched by earlier contraction of other parts of the atrial wall; these receptors may also discharge during atrial filling in late ventricular systole or diastole. Receptors which discharge only during ventricular systole must lie in parts of the atrial wall not stretched during atrial contraction. Atrial receptors have been classified according to their particular pattern of impulse discharge but it should be remembered that no anatomical or functional differences have been demonstrated. Discharge from atrial receptors depends primarily upon atrial filling but is also affected by factors affecting the contraction of the myocardium.

There is no good histological evidence of the existence of specific end structures in the ventricles but some impulses have

been recorded in the vagus nerves which probably arise from nerve endings in the ventricle. These receptors are stimulated during ventricular contraction especially in the isovolumic phase and are also strongly stimulated by veratrine and veratridine. The impulses travel in smaller fibres than those from the atrial receptors.

Sensory nerve endings exist in the adventitia and outer muscular layer of the posterior and caudal aspect of the arch of the aorta. An increase in the rate of discharge of impulses from the endings occurs when the pressure in the aorta rises. Their activity is determined not only by the mean pressure in the aorta but also by the rate of change of pressure. In common with other vascular receptors these nerve endings are stimulated by distortion of the aortic wall rather than absolute pressure and their activity may be modified by mechanical changes in the chest or by changes in intrathoracic pressure. Similar nerve endings exist in the right and left pulmonary arteries.

Sensory nerve endings in the lungs discharge in response to inflation or deflation of the lungs but their activity may be modified by pulmonary congestion and some fibres from the lungs show a cardiac rhythm.

CHAPTER II

THE EFFECTS OF MANOEUVRES LIKELY TO CAUSE CHANGES IN INTRATHORACIC BLOOD VOLUME.

It has been shown that sensory nerve endings exist in several sites in the intrathoracic vascular system where they may be affected by changes of intrathoracic blood volume. Evidence will now be examined which suggests that intrathoracic blood volume may change as a result of a variety of manoeuvres. Such volume changes are often accompanied by other cardiovascular changes and there may be alterations in heart rate, cardiac output and in the peripheral circulation. A theory that distension of the intrathoracic circulation induces changes in urine flow will be discussed later, but when considering this theory it is important to realize that changes of intrathoracic blood volume do not occur in isolation. It is the purpose of this chapter to examine in detail the effects of certain manoeuvres thought likely to cause changes of intrathoracic blood volume and, if possible, to account for these effects in terms of known physiological mechanisms.

A. INFUSION.

Bainbridge (1915) found that intravenous infusions of saline or defibrinated blood into anaesthetized dogs caused an acceleration of the heart. In his experiments the rate of infusion was

controlled to avoid marked changes in systemic arterial pressure although the increase in venous filling of the heart did cause a rise of venous pressure. The rise of venous pressure was usually sufficient to cause dilatation of the heart as indicated by the cardiometer but in one experiment illustrated in his paper arterial pressure had also risen by about 40 mm Hg. The degree of acceleration was reduced after cutting the rami accelerantes and after atropinization;no further acceleration could be obtained after cutting the vagus nerves. He attributed the cardiac acceleration mainly to a reduction in vagal inhibitory activity and partly to an increase in cardiac sympathetic activity; the suprarenal glands were not essential for the production of the changes. Since acceleration was associated with a rise of venous pressure and began when the rise of venous pressure was sufficient to cause cardiac dilatation, Bainbridge concluded that the tachycardia was caused by impulses arising in the heart and that the effective stimulus was a rise of venous pressure.

It has been suggested that cardio-acceleration is initiated from receptors in the venae cavae and pulmonary veins (Nonidez, 1937). Whilst there can be little doubt that intravenous infusions do cause an increase in the discharge of impulses from these receptors (Jarisch & Zotterman, 1948; Henry & Pearce, 1956) it has not been possible to show that these receptors form the afferent limb of a cardio-accelerator reflex and the evidence is conflicting that acceleration is always associated with intravenous infusions.

Meek & Eyster (1922) gave intravenous infusions of large volumes of saline, acacia, or blood over about an hour to anaesthetized dogs. Although the heart rate usually increased, the acceleration was inconstant and seldom large. After infusions of up to 100% of the blood volume haemoglobin determination indicated that much of the fluid was retained in the cardiovascular system but the diastolic size of the heart as judged from X-Ray did not permanently increase. Photomicrographs showed dilatation of the capillaries and venules of the ear, but accumulation of fluid in such vessels did not appear to provide an efficient reservoir which would protect against acute changes in blood volume, since haemorrhage of 10% of the blood volume still caused a decrease in heart size.

The use of mean arterial pressure records in the study of cardiovascular reflexes was criticized by De Graff & Sands (1925) who showed that mean pressure recorded from a mercury manometer gave no indication of either the actual level or the trend of systolic or diastolic pressures recorded from an optical manometer. Infusions of saline, 500 - 700 ml. at 100 ml./min, into anaesthetized dogs caused a large increase in pulse pressure with the diastolic pressure usually falling. This fall in diastolic pressure did not occur after repeated infusions or with infusions after haemorrhage; the authors suggest that it may be due to a lowering of blood viscosity in these circumstances. Cardiac acceleration occured only in 50% of their experiments and they claim that acceleration also occurred in response to infusions after vagotomy in one third

of their experiments, but these latter changes were very small. When the heart rate did increase it was not directly related to venous pressure.

Many authors including Bainbridge (1915) have noted the difficulty in eliciting cardiac acceleration when the heart rate is rapid initially. Warthen (1935) induced a slow heart rate in anaesthetized dogs by injecting morphine and found that infusion of saline or dextran produced a marked cardio-acceleration when the initial heart rate was less than 100 beats/min.

Infusions of saline or dextrose in saline always caused a rise of both peripheral and pulmonary venous (left atrial) pressure (Yeomans, Porter & Swank, 1943) which fell promptly after infusion was stopped. Arterial blood pressure usually rose during infusion (2-6 ml./kg/min) as did cardiac output; the greatest rise in cardiac output occurred during the first few minutes of infusion and the rise often persisted for as long as 10 min after completion of the infusions although venous pressure had usually returned to normal by that time. When pentobarbital anaesthesia was used the heart rate was rapid and variable both before and after infusion but with chloralose anaesthesia the heart rate was slow, with sinus arrhythmia and increased when infusions were given. The rapid stabilization of venous pressure after the infusion was attributed to the continued high cardiac output, loss of fluid from the vascular system and an increase in the capacity of the system.

Essentially similar changes have been observed in trained

unanaesthetized dogs (Raisz, Anslow & Wesson, 1950). Infusion of a modified Ringer-Locke solution, 200 ml./min for five minutes caused a rise in venous pressure which reached a peak before completion of the infusion. Venous pressure decreased rapidly after infusion and systemic pressure and heart rate were normal within 30 min although even after 70 min plasma volume was still 20% higher than the pre-infusion volume.

Rapid infusion of blood or saline causes an increase in left ventricular end diastolic pressure, stroke volume, stroke work and cardiac output in both the open and closed chest dogs (Ferguson, Shadle & Gregg, 1953), but changes in heart rate are more variable. In these experiments with dial-urethane-pentobarbital anaesthesia the initial heart rate in open chested animals was about 180 beats/min and there was little change with infusion; in dogs with an intact chest the initial rate was about 60 beats/min and infusion usually caused an increase.

Coleridge & Linden (1955) used a variety of anaesthetic agents to obtain a slow initial heart rate in dogs. Infusions of saline or dog blood were given either as small volumes rapidly (50 ml. in 10 sec) or larger volumes more slowly (200-400 ml. in up to 4 min). Changes in heart rate observed were related to two factors; firstly, large infusions were more successful than small ones in producing changes; secondly, if a change in rate occurred its direction and extent was determined by the initial heart rate, cardiac acceleration occurred if the initial rate was low whereas slowing occurred when the initial rate was high (over 150 beats/min). The changes could

not be related to systemic arterial pressure, respiration or to the character of the fluid infused. Infusion always caused an increase in mean right atrial pressure but the maximum increase in heart rate occurred about 90 secs after the end of infusion when right atrial pressure had fallen almost to the pre-infusion level. However Coleridge & Linden (1955) emphasize that to investigate the possible relationship between atrial pressure and the adequate stimulus for cardiac acceleration measurements must be made of dynamic effective atrial pressure.

Most investigators have found that venous pressure falls rapidly to normal levels after infusion but Henry, Gauer & Sieker (1956) suggest that there may still be some elevation of venous pressure after infusion of blood into anaesthetized dogs. These authors infused or bled up to 30% of the blood volume and after 10-20 min recorded pressures in the right atrium, pulmonary artery, left atrium and femoral artery; they regarded left atrial pressure as corresponding to left ventricular diastolic pressure. The changes in right atrial pressure, pulmonary artery pressure and left atrial pressure were in the same direction and they considered this portion of the cardiovascular system to behave as a single functional unit. As a result of the 60% total change in blood volume left ventricular diastolic (left atrial) pressure was altered by 14.8 cm H_2O.

The results of all experiments of infusions of either blood or plasma into dogs are complicated by the observation that with such infusions there is often a very rapid loss of the plasma infused.

Guyton, Lindley, Touchstone, Smith & Batson (1950) showed that with massive infusions of up to 1.6 times the animal's blood volume as much as 63% of the infused blood volume or 113% of the plasma infused was lost from the circulation within 40 minutes. The results indicated that the fluid leaving the plasma carried with it a relatively large concentration of protein. Their results were interesting in that even with such massive infusions blood pressure reached a plateau only 17 mm Hg higher than the pre-infusion level. Denervating the carotid sinuses and cutting the vagus nerves resulted in blood pressure rising to 54 mm Hg above control levels but a plateau was reached which did not increase with continued infusion. Similarly in one animal with complete spinal anaesthesia a plateau was reached 70 mm Hg below control levels. It is suggested from these results that arterial blood pressure is determined by two factors; firstly, the level of blood pressure resulting from the intrinsic adjustment of the capillary bed to the volume of blood, which sets the capillary pressure at a relatively constant level, and secondly the vasoconstrictor and cardiac excitor factors either nervous or humoral which may set the arterial pressure at a higher level; the first of these factors is often ignored. Similar loss of plasma volume and protein in dogs following transfusion has been reported by several authors (Huggins, Deavers & Smith, 1958). More recently work by Bliss, Johns & Burgen, (1959) has shown that plasma loss occurs when dogs are transfused with plasma from other dogs but not when transfused with their own plasma. Following infusion of 20 ml.plasma/kg at

a rate of 1 ml./kg/min, plasma volume expansion after 45 min was only 50% of the volume transfused. This effect was accompanied by cutaneous wheals and leakage of fluid particularly into the soft tissue of the face. The skin reaction and some of the plasma loss was reduced by administration of antihistaminic drugs. The results of Remington & Baker (1959) amply confirm these observations. Infusion of the dog's own blood led to the expected expansion of plasma volume followed only by some loss of protein free fluid and increase in specific gravity of the plasma. Infusion with plasma from other dogs led to a marked loss of whole plasma.

These findings have several implications and an unexpected variable is introduced into the design of experiments in which blood volume is artificially increased. Suggestions that the rapid loss of fluid and protein following an infusion is an important regulating factor in controlling the amount of blood in the circulation (Huggins, Deavers & Smith, (1958) can no longer be accepted. The finding that the dog's own plasma is completely retained within the circulation for at least an hour shows the correction of hypervolemia by this means is in fact surprisingly slow.

The many studies which have been made of the effects of infusion into conscious human subjects only emphasize how rapidly cardiovascular adaptation to the increased volume occurs. Eyster & Middleton (1924) found that infusion of about 10% of the blood volume in 10-15 min into anaemic patients did not lead to any significant change in heart size as judged from radiographs or to any change in heart

rate. Infusion does however cause an increase in venous pressure and Warren, Brannon, Weens & Stead (1948) by infusing rapidly (up to 70 ml./min) large volumes of saline or human albumin in saline have produced rises of right atrial pressure of up to 13 cm H_2O although this occurred with little change in heart rate. Following infusions of saline, plasma or blood there is a prompt fall in venous pressure to little above normal levels which are usually reached within an hour. (Murphy, Correll & Grill, 1941; Loutit, Mollison & van der Walt, 1942). Altschule & Gilligan (1938) observed a diffuse flush of the skin following infusions and attributed this is vasodilation; Harrison & Wilson (1950) considered that the prompt fall in systemic arterial and venous pressures after infusion is the result of vasodilatation. However Gauer, Henry & Sieker (1956) infused about 500 ml. blood into conscious human subjects and found that although central venous pressure did fall rapidly after the infusion it was still about 3cm H_2O above control levels after an hour. They suggest that the discrepancy between this finding and those of other workers may be due to changes in the visco-elastic properties of the veins accompanying stress, although this would hardly account for such a consistent difference. Their method of estimating central venous pressure by recording pressure from a vein in a dependant arm (Gauer & Sieker, 1956) might give erroneous results if there were changes in blood flow associated with vasodilatation in the limb.

Cardiac output is increased during intravenous infusions but

falls rapidly to normal levels after infusion (Witham, Fleming & Bloom, 1951). They also noted an increase in pulmonary arterial pressure, and Doyle, Wilson, Estes & Warren (1951) found that infusions of saline increased both pulmonary artery pressure and pulmonary wedge pressure and that normal pressure gradients were maintained from the peripheral veins to the left atrium. Cardiac output was not permanently increased and they concluded that there was an increase of blood volume in the pulmonary circulation. Sharpey-Schafer & Wallace (1942) had reported a decrease in vital capacity and an increase in the lung vascular marking on X-ray following large infusions of saline.

Only Harrison & Wilson (1950) have reported consistent increases in pulse rate following large rapid infusions. Several of their subjects subsequently showed a rise of temperature and developed urticaria and all were said to be anxious, but the maximum changes in heart rate did occur at the same time as completion of the infusion.

B. HAEMORRHAGE.

The effects of haemorrhage on the circulation were reviewed by McDowall (1938) whose work gives an extensive bibliography of the early observations. Although haemorrhage was usually associated with cardiac acceleration the exact mechanisms by which this was brought about were not clear; a small haemorrhage caused only a temporary fall of blood pressure which sometimes not only

recovered but occasionally rose above its original level; with larger haemorrhages the fall in blood pressure usually persisted. The recovery of blood pressure was thought to be brought about by a combination of effects, in addition to increased cardiac activity there was increased respiratory rate and depth and vasoconstriction of peripheral vessels.

The variations in the response of blood pressure and pulse rate to haemorrhage was to some extent clarified by the report of Grant & Reeve (1951) on war casualties. The blood pressure was found to be generally related to blood volume but three circulatory patterns were described. A normal blood pressure was associated with a normal colour and a normal pulse rate in two-thirds of cases and in one-third with a rapid pulse; occasionally the blood pressure was raised with either a slow, normal or fast pulse rate; with a low blood pressure the pulse was usually rapid. The first two patterns were associated with blood volumes about 70% normal whilst the last pattern was indicative of greater blood loss. The pulse rate was however considered a better indication of blood loss than blood pressure. If the blood pressure was greater than 100 mm Hg and the pulse rate normal then there was less than 20% blood loss. With blood volumes between 80-70% normal the blood pressure may be normal but the pulse rate was usually rapid. Below 70% normal volume pressure was low and pulse rapid.

The technique of catheterizing the heart in unanaesthetized men has made possible the study of right atrial pressures following loss of blood volume. The studies on shock of McMichael

(1944) suggest that a loss of about 20% of the blood volume will lead to a fall of about 6 cm H_2O in right atrial pressure. A smaller fall of only 2cm H_2O was observed by Brannon, Stead, Warren & Merrill (1946) although the blood loss in their cases was probably greater; These greater volume losses may have induced changes in venous tone. In earlier experiments in which they deliberately bled volunteers these authors (Warren, Brannon, Stead & Merrill, 1945) found a fall of 4cm H_2O after a loss of 300-900 ml. blood; this was in the absence of any change in heart rate or cardiac output; they also noted that with fainting the venous pressure rose towards normal. Henry, Gauer & Sieker (1956) found similar changes in pressure in the right atrium, pulmonary artery, left ventricle and systemic arteries of anaesthetized dogs which were bled in stages.

Changes in cardiac output usually follow a pattern similar to blood pressure and heart rate and the effect of a haemorrhage on cardiac output is by no means predictable. Whilst there is usually a fall with moderate blood loss there may be no change (Warren, Brannon, Stead & Merrill, 1945) and Sjostrand (1953) points out the constancy that cardiac output may show in spite of blood loss, regarding this as an indication that the body holds a certain blood volume in reserve. However McMichael & Sharpey Schafer (1944) measuring cardiac output by the direct Fick method found a 20% fall in cardiac output when 420 ml. blood were removed by venesection, and at the same time right atrial pressure fell 2-3 cm H_2O. Ralston, Cobb & Bruce (1961) using indicator dilution

curves found a significant decrease in cardiac output and stroke volume when 500-900 ml. blood was removed. Their calculations indicated that central blood volume was reduced by the same proportion as the systemic circulation but there is doubt about the validity of calculating central blood volume from an equation using cardiac output.

Many early studies have indicated that after haemorrhage body fluids enter the cardiovascular system to replace the lost volume (Meek & Eyster, 1921) and it is known that this process may occur rapidly in the anaesthetized dog (Allen, Walzer, Gregerson & Gregerson, 1959). However the work of Ebert, Stead & Gibson (1941) casts doubt on the extent of such replacement occurring in conscious human subjects. Six normal subjects were bled between 15-20% of their blood volume in 6-13 min, five developed circulatory collapse but the replacement of fluid in these subjects was similar to that in the other subject who showed no symptoms. Before collapse there was little change in blood pressure or heart rate but after collapse both systolic and diastolic pressures were low and heart rate was slow as in a typical vaso-vagal faint. The plasma volume during the first 36-111 min after haemorrhage increased by only 145-230 ml. although 760-1070 ml. had been removed. The increase in plasma volume was accompanied by a decrease in serum protein concentration and was therefore the result of an addition of a protein poor fluid to the blood stream. After this initial dilution plasma protein concentration did not fall and therefore all further increase in volume was accompanied by an addition of plasma protein.

Plasma volume was normal in 24 hrs and then elevated by about the volume of the missing red cells in 2-3 days. A large increase in plasma volume was not maintained even when saline was given, until the amount of circulating protein was increased.

Haemorrhage was considered by Henderson & Haggard (1922) to present symptoms very similar to those seen in asphyxia. They were particularly interested in the increase in respiration associated with haemorrhage and point out that a 100% increase in respiratory volume may occur unnoticed unless measurements are made. They showed that following a severe haemorrhage there was a progressive fall in plasma carbon dioxide combining power which indicated the development of a metabolic acidaemia. After muscle trauma which may reduce blood volume by as much as 40%, or after haemorrhage, oxygen consumption decreases and arterio-venous oxygen content difference increases (Root, Walcott & Gregersen, 1947). At the same time cardiac output measured by the direct Fick method decreased, in particular when peripheral circulatory failure developed the cardiac output became very low (10-25% of normal). When conscious dogs are subjected to a reduction of blood volume of between 30-40% either by haemorrhage or muscle trauma there is a progressive decrease in both pH and arterial CO_2 content. (Root, Allison, Cole, Holmes, Walcott & Gregersen, 1947). Allison, Cole, Holmes & Root (1947) state that blood flow is slowed after haemorrhage but give no detail of these experiments.

The difficulty sometimes experienced in efficiently respiring subjects who have suffered severe blood loss may depend upon changes in the pulmonary circulation (Gerst, Rattenborg & Holaday, 1959).

They removed about one-third of the blood volume from anaesthetized dogs, systemic arterial pressure decreased progressively with the decrease in blood volume but pulmonary arterial pressure fell to about two-thirds of the control value and then remained steady despite further blood loss. The respiratory dead space increased following haemorrhage and there developed a marked CO_2 tension gradient between arterial blood and end tidal gas indicating significant alveolar dead space. With intermittent pressure ventilation in these experiments it seems likely that reduction of pulmonary blood flow may lead to complete closure of portions of the pulmonary vascular bed. Thus whilst arterial blood will have a normal oxygen content the reduced flow in the peripheral circulation will lead to a decreased venous oxygen content and raised venous pCO_2 and also there will be a wide difference between arterial pCO_2 and CO_2 partial pressure found by sampling alveolar air.

The part played by the carotid and aortic baroreceptors and chemoreceptors in the circulatory and respiratory adjustments after haemorrhage was discussed by Neil (1954). In his view maintenance of blood pressure and cardiac output after a loss of blood volume depends largely upon the activity of baroreceptors. Head, Green & Neil (1952) have shown that the baroreceptors are more powerfully affected by a pulsatile pressure than a steady one and Neil (1954) suggests that the vasoconstriction necessary to maintain mean blood pressure at about normal levels is the result of a diminished stimulus to the baroreceptors consequent

upon a reduction in pulse pressure.

The effects of these carotid reflexes resemble those of the injection of noradrenaline, which may be released either from adrenergic neurones or from the suprarenal glands (for bibliography see von Euler, 1951). Armin & Grant (1955) demonstrated an increase in vasoconstrictor activity in rabbit blood and plasma after rapid bleeding of about one-third of the blood volume; adrenalectomy considerably reduced but did not abolish this constrictor activity; Watts (1956) and Walton, Richardson, Walton & Thompson (1959) have found marked increases in plasma adrenaline levels in dogs subjected to acute haemorrhagic hypotension. The concentrations found were sufficient to cause intense peripheral vasoconstriction.

Neil (1954) considers that peripheral circulatory failure occurs when the compensatory mechanisms are inadeqate to maintain sufficient blood supply to maintain the brain stem centres; failure of these central cells will abolish vasoconstrictor activity as evidenced by a fall in peripheral resistance and a profound fall in blood pressure.

C. ORTHOSTASIS AND CUFFING.

Orthostasis involves changing from the recumbent to the upright posture and brings the force of gravity to bear upon the vascular bed. In man the distance from the thorax to mid-thigh is approximately 90 cms, thus a pressure head of 90 cm H_2O develops in the thigh veins which in recumbency are distended by at most

20 cms H_2O; the legs can accommodate very considerable amounts of blood at such pressures. It involves a retention of a certain proportion of the circulatory blood volume to bring the pressure in the veins to the value needed to return the blood to the heart, this blood is no longer available to the circulation so that there is a reduction in 'effective blood volume' (Landis, Brown, Fateux & Wise, 1946).

The effects of gravity on the circulation were examined by Hill & Barnard (1897) who were well aware of the hydrostatic forces acting on the column of blood in the veins on the assumption of the erect posture. However, they regarded the effects of hydrostatic pressure on the circulation in the lower limbs as insignificant when compared with the effect on the abdominal vascular area (Hill, Barnard & Sequeira, 1897). Sjostrand (1952) has shown that in conscious human subjects with good muscle tone, the abdomen does not change contour significantly on standing, the veinswithin are protected by the fluid counter-pressure of the viscera from the distending effect of the hydrostatic pressure.

There can be no doubt that in the passive erect posture blood is pooled in the lower limbs and Asmussen, Christensen & Neilsen, (1940) have found ~~that~~ with a plethysmograph an increase in volume as much as 475 ml. in one leg with a 45° tilt. This volume includes blood which is pooled rapidly in the veins as a result of the altered hydrostatic pressure and also fluid lost from the vessels. The latter loss accumulates over about 30 min. and leads to an increase in the concentration of plasma protein (Thompson, Thompson & Dailey,

1928). These authors estimated that as much as 110 ml. of protein free fluid was lost from each litre of plasma, a finding confirmed by Waterfield (1931). Thus the combination of blood pooling and loss of fluid from the vascular system when the subject remained still and with muscles relaxed could lead within a few minutes to a total fluid loss to the circulation of about 1000 ml; an amount sufficient to induce very definite readjustments in the cardiovascular system.

A decrease in vital capacity occurs when a subject lies down (Hamilton & Morgan, 1932) and this decrease is eliminated by first placing venous occlusion cuffs on the thighs. Since this experiment was open to criticism on the grounds that movement of the ribs and diaphragm might be more difficult when lying, Dow (1939) tried the experiment of placing cuffs on the thighs of recumbent subjects and inflating to diastolic pressure. The resultant 170 ml increase in vital capacity was evidence that the results of the earlier experiment were not due solely to mechanical difficulties with breathing. Sjostrand (1952) has studied the distribution of blood in more detail. He measured leg blood volume using a plethysmograph, the trunk he enclosed in another plethysmograph consisting of a rubber bladder enclosing the thorax and abdomen but not the buttocks, the volume of air in the lungs was measured by inhaling hydrogen using a Knipping apparatus and measurements of heart size were made by X-ray. The vital capacity did not show as great a change as the total pulmonary capacity and for this reason when used alone led to an underestimation of the contribution of blood by the thorax. He collected blood in the lower limbs by standing for 20 min and

then applied occlusion cuffs. These were taken off in recumbency producing an increase in trunk volume and a decrease of the volume of air in the lung. He estimated that 78% of the volume of blood transferred from the legs goes to the thorax. After 20 min standing both thoracic and heart blood volume decreased 25% whilst the systemic circulation lost only 2.7% of its volume. The shift of blood from the legs to the thorax on recumbency has been illustrated in another way by Tenney (1959) who showed there was a continuous headward displacement of the centre of gravity of the body for 20-30 min after lying down; there was no change of the centre of gravity in a legless man.

It is likely that there is a redistribution of blood within the lungs themselves associated with changes in posture. Mattson & Carlens (1955) using a specially designed catheter, measured ventilation and oxygen uptake simultaneously in the upper and two basal lobes of the right lung; when the subject changed from a supine to an erect position there was little change in ventilation but an appreciable decrease in oxygen uptake in the upper lobe. Riley, Permutt, Said, Godfrey, Howell, Shepard, Cheng (1959) extending these observations found the alveolar dead space to be greater in the standing than supine position. These findings are consistent with the hypothesis that the apex of the lung is virtually non-perfused in the resting human subject in the upright posture, the decreased perfusion probably being orthostatic in origin.

The changes in pulse rate occurring on changing from a lying to a sitting or standing position were examined carefully by MacWilliam

(1933). An increase on changing from lying to sitting was attributed to the change in position of the carotid sinus relative to the heart. When a change from sitting to standing was made, although there was no change in blood pressure the heart rate again increased. This increase was prevented by first applying arterial occlusion cuffs to the lower limbs, or by squatting and the pulse rate was also slower when the legs were moved slowly. He concluded that these pulse rate changes were not mediated through an alteration in blood pressure in the sino-aortic area, since this apparently remained unaffected, but originated from some other part of the vascular apparatus under the influence of the hydrostatic factor. This hypothesis was supported by Edholm (1940) who carried out experiments on the cat. One carotid sinus was denervated and the other carotid artery clipped; the blood pressure response to tilting was then normal as compared to the cat with only one carotid sinus denervated. Cutting the vagus nerves led to a marked fall in blood pressure on tilting. Whilst these experiments indicate that compensation can occur in the absence of changes in carotid sinus stimulation they do not provide evidence that the carotid sinus baroreceptors are not normally concerned in the compensatory response to tilting. Mayerson (1942) supported this latter view, using lightly anaesthetized dogs denervation of the carotid sinus diminished the ability to compensate for gravitational changes.

Whilst there may be little obvious change in blood pressure on assuming an erect posture most investigators have found a decrease in cardiac output occurs. McMichael (1937) measured cardiac output

using acetylene and found a fall when changing from a supine to an erect position and in addition an increase in the arterio - venous oxygen content difference. More recently Bevegård, Holmgren & Jonssen (1960) using the direct Fick method to estimate cardiac output have found a decrease of as much as 2 l./min, since pulse rate increased there was a decrease in stroke volume of 40% which they attribute to impaired diastolic filling as a consequence of the shift of blood to the legs. The heart volume has been shown to be larger when lying than it is when erect (Linderholm & Strandell, 1958) and Kondo & Katz (1945) showed heart size was reduced by venous occlusion of the hind limbs of the dog even when a constant heart rate was maintained.

Pooling of about 700 ml. of blood in the lower limbs causes a fall in right atrial pressure of about 5 cm H_2O (Warren & Stead, 1943). Since similar changes have been observed in peripheral venous pressure there is little change in the pressure gradients between the right atrium and other parts of the venous system.

A decrease in right atrial pressure and cardiac output was found by Brigden, Haworth & Sharpey-Schafer (1950) when human subjects were tilted from a supine to an erect posture and there was a decrease in forearm blood flow as measured by venous occlusion plethysmography; the decrease in forearm blood flow did not occur in a sympathectomized arm when blood pressure was maintained. The urinary excretion of adrenaline and noradrenaline has been estimated by von Euler, Luft & Sundin (1955). When healthy human subjects were tilted to 75° for three hours there was a steady rise in the

excretion of adrenaline and especially noradrenaline. During the first few minutes blood pressure fell by 10-15 mm Hg, the systolic pressure then returned to normal, the diastolic pressure to a little above normal, and the pulse rate increased by 15-25 beats/min. They considered their findings were in agreement with the supposition that blood pressure homeostasis in standing is maintained by a reflex stimulation inducing noradrenaline secretion from vasomotor nerve endings and possibly the adrenal medulla. A significant rise in plasma catecholamine levels on tilting to 60^{o} was found by Hickler, Well, Tyler & Hamlin (1959). When patients suffering from postural hypotension were used the blood pressure fell very low but there was little change in heart rate and no change in adrenaline concentration was found. Their method did not strictly analyse adrenaline and noradrenaline but they claim their results are valid since they were comparing acute changes.

The composition of the blood of rabbits subjected to gravity shock was studied by Cole, Allison, Murray, Boyden, Anderson & Leathem (1944) who found changes very similar to those following haemorrhagic or traumatic shock. The rabbit is unable to compensate adequately for the accumulation of blood in the hind limbs when held vertically and there is a decreased venous return and cardiac output, a fall in blood pressure and an increased arterio-venous oxygen content difference. The slowed blood flow results in a decreased oxygen supply to the tissues and a decreased blood supply to the kidneys. Stagnant hypoxia leads to decreased

oxygen utilization and metabolic acidosis develops, lactate and pyruvate accumulate and there is a striking fall in pH from 7.33 to 7.0; there is liberation of inorganic phosphate which is not excreted because of the depressed renal function. These changes, which are typical of peripheral circulatory deficiency with tissue anoxia, are reversed if recovery occurs.

D. POSITIVE AND NEGATIVE PRESSURE BREATHING.

Flying at high altitudes has made it necessary to be able to breath oxygen supplied to the lungs at pressures greater than those of the surrounding atmosphere. This need has stimulated research into the cardiovascular and other effects of such positive pressure breathing and observations have also been made on the effects of breathing from a reservoir at a pressure less than that surrounding the body (negative pressure breathing). It has long been recognised that changes in the cardiovascular system occur along with respiratory movements. Brecher (1956, p.6) reviewed the early work on this subject and distinguished between two effects of the respiratory movements on venous return. Firstly, the continuous elastic traction of the lungs creates a negative intrathoracic pressure and thus favours venous return by producing a pressure gradient between the peripheral venous capillaries and the heart. Secondly, the dynamic effects of changes in intrathoracic pressure which occur during spontaneous respiration, artificial respiration or other voluntary or involuntary respiratory manoeuvres may also influence venous return. Under normal physiological conditions

static and dynamic effects are combined in their actions on the return flow of blood but can be separated experimentally and theoretically.

Hill, Barnard & Sequeira (1897) demonstrated that a rise of intrathoracic pressure raised venous pressure and lowered arterial tension. Hill & Barnard (1897) raised intrathoracic pressure by positive pressure artificial ventilation in the dog and showed that if the animal was then tilted into a hind limbs down posture arterial pressure was reduced to zero, if the abdomen was compressed there was a temporary rise of pressure as blood was forced from the abdomen to the chest. Changes in cardiac output occurring during respiratory obstruction were first measured by Huggett (1924). He used anaesthetized cats and made them breathe from a bottle provided with a water valve, so that there was either 5 cm H_2O obstruction to inspiration or 5 cm H_2O obstruction to expiration. With obstruction to inspiration therefore a pressure of 5 cm H_2O less than atmospheric pressure had to be developed in the chest before inspiration occurred; under these conditions cardiac output measured by the direct Fick method increased by about 30% the increase being mainly in stroke volume as heart rate was little affected. With obstruction to expiration a fall in cardiac output of about 30% was found.

The effects of positive pressure breathing on the circulation were studied by Werko (1947) whose work should be consulted for a review of the subject. The most consistent change found in both animal experiments and studies in man was a decrease in cardiac

output, in some instances of up to 60%; the pressures used were usually greater than 10 mm Hg. Most of the papers examined attributed the decreased cardiac output to a decreased venous return to the right atrium (Holt, 1944; Humphreys, Moore, Maier & Apgar, 1938) although Beecher, Bennett & Bassett (1943) stressed that an increase in pulmonary vascular resistance might occur to which the changes could be ascribed. Werko (1947) himself made a careful study of cardiac output measured by direct Fick principle and blood pressure in human subjects exposed to intermittent positive pressure breathing, expiratory positive pressure breathing and continuous positive pressure breathing. In normal subjects intermittent positive breathing at a pressure greater than 5 cm Hg caused a fall in cardiac output which was greater the higher the pressure; with pressures below 5 mm Hg cardiac output was not significantly changed. There were only small changes in heart rate and blood pressure so that in those cases in which cardiac output fell there was an increase in calculated peripheral resistance. The decrease in cardiac output during pressure breathing was closely correlated to a decrease in 'net filling pressure' of the right ventricle (calculated as right ventricular end diastolic pressure minus intrapleural pressure). Pulmonary vascular resistance was also calculated but changes in resistance during pressure breathing did not show any correlation to changes in cardiac output.

Holt (1944) found a fall in cardiac output in anaesthetized dogs breathing air or oxygen from a weighted spirometer. Values for cardiac output measured by the direct Fick method showed wide

variations but with a dye dilution method variations in control values for cardiac output were small and there was a 33% fall in cardiac output with a positive airway pressure of 16 cm H_2O. At the same time the pressure drop from the peripheral veins to the right atrium was reduced by about 70%. Several authors have noticed that the fall in cardiac output is more severe after previous haemorrhage (Beecher, Bennett & Bassett, 1943). Carr & Essex (1946) found that whilst peripheral venous pressure was raised there was sufficient venous return to maintain an adequate cardiac output, but if blood had been lost by haemorrhage then there would be a further decrease in venous return and death due to inadequate cardiac output. Similar effects were seen after loss of blood into a traumatized limb. They also examined the beat to beat changes in arterial pressure during the respiratory cycle. Intermittent positive pressure ventilation was used; on inspiration (positive pressure of 20 cm H_2O applied) blood pressure increased for the first 2-3 beats and then fell sharply. When expiration began there was at first a further fall and then a rise to preinflation levels. Obstruction to venous return was demonstrated by an increase in jugular venous pressure and an increase in diameter of the abdominal part of the inferior vena cava as seen on X-ray.

Although there is agreement that cardiac output falls during positive pressure breathing there is much less certainty about the effect upon blood pressure. In general there is little change in blood pressure (Carr & Essex, 1946) but there may be an increase (Barach, Eckman, Ginsburg, Rumsey, Korr, Eckman & Besson, 1946) or a decrease (Beecher, Bennett & Bassett, 1943). In any

event the fall in systemic pressure is small compared to the fall in cardiac output and systemic vascular resistance is therefore increased (Lenfant & Howell, 1960). Fenn & Chadwick (1947) and Fenn, Otis, Rahn, Chadwick & Hegnauer (1947) have shown that positive pressure breathing causes a decrease in finger volume and in rate of blood flow through the finger. This decrease in blood flow was considered to be due to vasoconstriction rather than to the increased venous pressure. Although denervation of the carotid sinus and vagotomy does not eliminate the recovery of the blood pressure after positive pressure breathing is started the observed changes in blood pressure are affected by sinus and aortic reflexes (Sharpey-Schafer & Bain, 1932). The anaesthetic agent used may also affect the response of the cardiovascular system to positive pressure breathing; Price, King, Elder, Libien & Dripps (1951) studied this problem and described the typical effect in conscious subjects as a fall in arterial pressure followed by a gradual recovery, and an overshoot of the arterial pressure on release from positive pressure respiration. With light cyclopropane anaesthesia there was little recovery from the initial fall in pressure but with deeper anaesthesia there was no reduction in pressure and no increase in venous pressure. With sodium thiopentone anaesthesia (Price, Conner, Elder & Dripps,1952) there was a marked fall in arterial pressure but no recovery; the fall in arterial pressure was reduced by tilting into the head-down position. These authors suggest that anaesthetized subjects may be protected against the reduction in arterial pressure in two ways; venous pressure may be elevated, and transmission of the

airway pressure to the great veins may be reduced. Thus whenever central venous pressure is high, cardiac output should be better maintained in the face of high airway pressure as is the case in congestive cardiac failure. Diminished transmission might result from decreased tone in muscles or a decreased distensibility of the lung when turgid with blood. Right atrial pressure is elevated with cyclopropane anaesthesia; the vasomotor response may be inadequate in thiopentone anaesthesia.

The importance of abdominal muscular tone in the maintenance of systemic arterial pressure during high intrapulmonary pressures has been studied by Bjurstedt (1953). Dogs under light to moderate sodium pentobarbital anaesthesia were used and a continuous positive pressure of 20 cm H_2O used to inflate the lungs for short periods; the effect was similar to that already described. Bjurstedt believed that venous pooling in the abdomen contributed to the initial pressure drop and that the secondary recovery was assisted by an increase in abdominal tone. There was a gradual rise in the abdominal pressure which may have been due to either a gradual pooling of blood or to a prolonged expiratory effort by the abdominal muscles. Although there is no doubt that pooling of the blood in the abdomen is opposed by the tone of the abdominal muscles there is no evidence to support his postulation that the vagi might provide special reflex pathways which by controlling intrathoracic abdominal differential pressure maintain venous return under conditions of increased intrathoracic pressure.

Changes in the circulating plasma volume during positive

pressure breathing have been reported by Sobel, Marotta and Marbarger (1959). Plasma volume estimated by dye dilution decreased by 30% after breathing with a continuous positive airway pressure of 18.5 cm Hg for 160 min, although haematocrit readings indicated only a 13% reduction in plasma volume. Kilburn & Sieker (1960) measured plasma volume by dilution of I^{131} labelled albumin but were unable to show any change with continuous positive pressure breathing at 26 cm H_2O. These authors found cardiac output decreased 39% but this effect was reversed by hyperventilation. They suggested that even in the presence of a high positive airway pressure hyperventilation is able to effectively improve aspiration of blood to the right side of the heart.

There have been relatively few studies of the effects of negative pressure breathing on the cardiovascular system. Pressure in the right atrium and peripheral veins of anaesthetized dogs breathing from a chamber at -20 cm H_2O pressure were measured by Holt (1941). He found that when there was a marked fall in right atrial pressure peripheral venous pressure remained constant. Holt (1944) extended these observations and found that with negative pressure breathing at -16 cm H_2O the pressure gradient from the peripheral veins to the right atrium increased by about 200%. In spite of this there was no change in cardiac output and he suggested that the high pressure gradient was due to collapse of the veins just before entry into the chest providing resistance to the flow of blood. In conscious human subjects however, his experiments (Holt 1943) indicated that the veins do not collapse

when the negative airway pressure is less than 14 cm H_2O. This is apparently because the right atrial pressure in the supine human subject is several centimetres of water above atmospheric and a high negative pressure is therefore required before collapse occurs. When he decreased airway pressure gradually to-40 cm H_2O peripheral venous pressure decreased at first but then became constant presumably because of collapse of the veins.

The evidence that inspiration increases right atrial inflow is discussed by Opdyke, van Noate & Brecher (1950), and Brecher (1956, p.71) considers that during quiet inspiration in the recumbent position the extrathoracic veins should not collapse to such an extent as to throttle venous return. During deep and prolonged inspiration the extrathoracic veins should, after their depletion, enter the collapsed stage and prevent a further augmentation of venous return. Thus if collapse occurs there will be no further increase in venous return or cardiac output with negative pressure breathing. During normal spontaneous respiration venous return in both the superior and inferior venae cavae is augmented by the inspiratory movements as a result of both abdominal compression and thoracic suction.

Gauer, Henry, Sieker & Wendt, (1954) measured cardiac output in one anaesthetized dog with 10 cm H_2O negative pressure breathing. They agreed with Holt's (1944) finding that cardiac output was unaltered, the average mean blood pressure did not change, but heart rate doubled and the rate of respiration on the average tripled with the onset of negative pressure breathing; these

changes occurred almost instantaneously. These authors suggest that the most obvious effect of negative pressure breathing on the circulation is an engorgement of the heart and lung region although there is little direct evidence for this assumption. Mills (1949) estimated that in man there was a decrease in vital capacity of 300 ml. immediately after a period of negative pressure breathing and suggests this is due to the accumulation of blood in the lungs. However Rahn, Otis, Chadwick & Fenn, (1946) did not find any change in vital capacity with positive pressure breathing and with negative pressure breathing there was a 10% decrease in vital capacity only in the supine position. Kilburn & Sieker (1960) found no significant changes in central blood volume in seven human subjects during negative pressure breathing.

The cardiovascular response of man to negative pressure breathing at pressures down to -30 cm H_2O have been recently studied by Ting, Hong & Rahn (1960). Systolic and diastolic pressures and heart rate were unchanged although finger plethysmography indicated peripheral vasoconstriction of a similar degree to that seen with positive pressure breathing. Sieker, Gauer & Henry (1954) had also reported in conscious human subjects that negative pressure breathing led to no change in pulse rate, arterial pressure, measured occasionally with a standard sphygmomanometer, or respiratory rate. Such measurements would not detect moderate changes in pulse pressure or respiratory variations in arterial pressure which are accentuated during negative pressure breathing (Kilburn & Sieker, 1960). The latter

authors also found that negative pressure breathing of -20 cm H_2O in normal man increased cardiac output and stroke volume and to a less extent the size of the heart. They used a dye dilution method to estimate cardiac output whereas other workers have employed the Fick method.

Lenfant & Howell (1960) using dogs anaesthetized with pentobarbitone found that cardiac output and systemic and pulmonary vascular resistances were unchanged during negative pressure breathing. Whilst pulmonary vessel and venae cavae pressure decreased this fall was not in parallel with the fall of intrathoracic pressure. They suggested these vessels may have reached the limits of their distensibility. It is of interest that they found a marked decrease of arterial blood oxygen concentration in spite of an oxygen tension of 300 mm Hg in the inspired air. They believe that atelectasis may develop and allow a spurt of mixed venous blood to enter the pulmonary veins. Their figures for the percentage of blood shunted are surprisingly large, at airway pressure of minus 15 cm H_2O it is estimated that 32% of the cardiac output is shunted whilst with a pressure of minus 24 cm H_2O 72% of the cardiac output may be shunted.

SUMMARY.

The effects of infusion into anaesthetized dogs and conscious human subjects are to increase venous return and cardiac output to a degree dependent upon the volume and rate of infusion and there may also be an increase in arterial pressure and in heart rate especially when the initial heart rate is slow. Cardiac output and pressures in the heart chambers and peripheral vascular system return rapidly to about normal levels after the end of infusion and certainly reach normal levels before the total blood volume decreases to its pre-infusion level. The blood volume may remain elevated by as much as 20% without any obvious effect upon vascular pressures or heart rate. The excess blood volume is accommodated in the peripheral and intrathoracic circulations.

Haemorrhage of less than 20% of the blood volume may cause little or no change in heart rate, arterial pressure or cardiac output. When haemorrhage is more severe blood pressure and cardiac output may fall and the heart rate increases, compensatory vasoconstriction occurs and there is release of vasoconstrictor substances. Entry of fluid into the vascular system is small compared to the volume lost, and this volume is only replaced as a protein containing fluid over the course of one to two days.

Orthostasis causes pooling of blood in the veins of the legs and also a loss of protein-free fluid from the vascular system. After standing for about half an hour the effective blood volume

may be reduced by as much as 20%. Cardiac output is reduced and there may be compensatory vasoconstriction accompanied by the release of vasoconstrictor substances.

Positive pressure breathing reduces intrathoracic blood volume and cardiac output and may cause an increase in plasma protein concentration. Changes in arterial pressure are small and there is peripheral vasoconstriction. Negative pressure breathing in chloralose anaesthetized dogs causes marked increases in heart rate and respiratory rate but in conscious human subjects these changes do not occur. Many workers have found only small increases in cardiac output with negative pressure breathing. The increase in cardiac output will be limited if venous collapse occurs and the greatest increase is therefore likely in conscious supine human subjects in whom the right atrial pressure is initially several centimetres of water. In the anaesthetized animal there may be some pooling of blood or the anaesthetic agent may induce cardiovascular changes leading to a low venous pressure so that venous collapse occurs more readily. Arterial blood pressure shows marked variations with respiration during negative pressure breathing although mean arterial pressure may show little change.

CHAPTER III.

A THEORY THAT STIMULATION OF INTRATHORACIC RECEPTORS MAY INDUCE CHANGES IN URINE FLOW.

A. INTRODUCTION.

Constancy of the internal environment was seen by Claude Bernard (1878) as the primary condition for freedom and independence of existence. This constancy was seen not as a static state but as an equilbrium established between the organism and its environment and the result of compensation occurring continually and exactly. Starling (1909) is usually attributed with having first pointed out that the organism must be provided with distinct mechanisms for the regulation of the amount, the composition and the molecular concentration of the fluids in the body. But Starling viewed such mechanisms as maintaining an average quantity and composition of the internal media of the body, not constancy of amount and composition. "Constancy of any bodily condition is unattainable in the presence of the varying conditions of our environment and is indeed not compatible with our conception of life. Not only must there be deviations from the average in respect to the total volume and molecular concentration of the fluid of the body, including in this term the blood, lymph and tissue fluids, but we may expect also to find variations in the distribution of these fluids, any one of them being increased or decreased at the expense of the others". However, the maintenance of an average volume of the

body fluids is a process necessary for preserving constant the conditions of life in the internal environment. Many authors have pointed out that if the kidney produces a litre of urine of the same freezing point as the blood, the volume of the body is diminished but the osmotic concentration unchanged. This does not necessarily mean that if volume is to be regulated this must be independent of osmotic pressure regulation (Henderson, 1916), as these two factors of volume and osmotic pressure are bound together in determining the environment (McLean, 1925). The concept that steady states in the organism must be maintained by complex coordinated physiological processes was developed by Cannon (1932), the existence of such steady states was called homeostasis and he envisaged a homeostatic mechanism maintaining each steady state. Cannon considered the prime assurance against extensive shifts in a steady state was the provision of 'sensitive automatic indicators' which would set in motion corrective processes at the very beginning of a disturbance. That such a mechanism exists to maintain the constancy of the crystalloid osmotic pressure of body fluid has been amply demonstrated by Verney (1947). It is now established that a reduction in plasma osmotic pressure affects osmoreceptors situated in the distribution of the internal carotid artery and leads to a diminished secretion of antidiuretic hormone from the neurohypophysis thus leading to a reduced renal reabsorbtion of water and so diuresis. Many authors have been encouraged therefore to look for a similar mechanism to regulate body fluid volume which would consist of the classical components, a sensory limb to register volume, integrating and

effector centres and finally the effector systems operating to restore to normal the signals from the sensing device (Pearce, 1961). Such a system would relate the urinary excretion of salt and water to cardiac output (Borst, 1948), blood volume or the fullness of some particular part of the circulation. Suggestions of sites of the sensory limb of the system have been numerous and the proposals have been fully reviewed by Smith (1957) and Grossman (1957); in particular Gauer et al. (1954) have advanced the idea that "volume receptors" exist in the intrathoracic part of the circulation. Before examining this proposal in detail it is as well to note that if there is a volume receptor there need not only be one and indeed it might be surprising if this function of body fluid volume, so important to the organism, were regulated by one simple mechanism (Welt, 1960). It may be more reasonable to approach the problem with the perspective that there may be many ways in which the kidney is notified of an error in volume and a variety of mechanisms by which the kidney may compensate for the error.

The work already reviewed in the preceding sections has indicated that considerable variations occur in the volume of blood in the intrathoracic part of the circulation. In fact Sjostrand (1953) has elaborated the hypothesis that this part of the circulation contains under resting conditions a reserve volume of blood which might be rapidly mobilized in response to displacements of blood, for example to the lower limbs in association with postural changes. Sjostrand (1953) viewed this reserve volume as being utilized during

physical work, the total blood volume being a decisive factor in determining physical working capacity. The concept that the intrathoracic circulation acts as a reservoir may however be questioned, as blood only collects in this part of the circulation in the recumbent posture. In fact it is apparent that the distribution of blood in the body depends upon gravitational forces, upon the distensibility of particular parts of the vascular system, and upon the blood volume rather than upon some particular part of the circulation acting as a reservoir. However, Gauer, Henry, Sieker & Wendt (1954) considered the pulmonary and venous circulation to be an appropriate unit for a potential reservoir, as measurements of pressure changes indicated that with moderate changes in blood volume in recumbent subjects, the pulmonary and venous circulation acted as a distensible container (Gauer, Henry & Sieker, 1956), and in spite of the interposition of the right ventricle, the systemic veins and lung bed acted as though they were one continuous system. On this hypothesis if there was to be an automatic indicator of volume the intrathoracic circulation and the systemic veins would be places in which such indicators might be situated.

Widespread acceptance of the idea that increased filling of the intrathoracic circulation is associated with increased urine flow, and oliguria with decreased filling of the intrathoracic circulation, has depended upon "a large number of observations in which this concurrence can be observed as a result of very different physiological events" (Gauer, Henry, Sieker & Wendt, 1954). Some

Procedure	Urine Flow	Intrathoracic Blood Volume	Comment
Haemorrhage	↘	↘	No change in urine except in 'shock':then fall g.f.r.
Pos. Pressure Breathing	↘	↘	Fall in g.f.r.
Orthostasis	↘	↘	Increase in plasma protein Fall in g.f.r.
Venous Cuffing	↘	↘	ditto
Infusion Hyperoncotic	↘	↗	Increase in plasma protein Fall in g.f.r.
Infusion Blood	↗	↗	Little effect on urine
Infusion Saline	↗	↗	Fall in plasma protein Increase in g.f.r.
Neg. Pressure Breathing	↗	↗	Small unexplained diuresis
Lying Down	↗	↗	Effects on Na excretion due to g.f.r. Small unexplained diuresis

Table 1. The behaviour of urine secretion in response to procedures changing the filling of the intrathoracic circulation. (After Gauer,Henry & Sieker, 1961)

of these events are listed in Table 1; as Gauer, Henry & Sieker (1961) point out this Table summarizes the available evidence that intrathoracic receptors control total blood volume. It has already been shown that sensory nerve endings exist in the intrathoracic circulation and that the impulse discharge from these endings may be modified by changes in intrathoracic blood volume. Manoeuvres known to cause changes of intrathoracic blood volume also have other effects upon the cardiovascular system. It is now proposed to examine the evidence that these manoeuvres cause urinary changes and to consider what agents might act on the kidney to produce such changes.

B. INTERPRETATION OF CHANGES IN URINARY EXCRETION.

Whilst changes in the volume and composition of the urine may be accurately measured, the interpretation of such changes in terms of agents acting on the kidney and intrarenal mechanisms (O'Connor, 1962) is more difficult. In the experiments to be discussed changes in renal function are frequently interpreted in terms of the renal clearance of substances such as inulin, diodrast and creatinine. However Davies & Shock (1950) and Mandell, Jones, Willis and Cargill, (1953) have estimated clearances of inulin and exogenous creatinine in successive urine collections and found the standard deviations of individual determinations from the mean of the series was 5 - 10%; these measurements were made under conditions intended to be ideal for the estimation of clearance values. The possible reasons for these differences and other hazards of the interpretation of clearances have been discussed in detail by Wesson (1957). Changes

in renal function are often interpreted on the basis of changes in the excretion of water and salt compared with changes in clearance estimations and Wesson (1957) has listed several criteria which form a basis for evaluating the significance of filtration rate measurements as related to sodium chloride excretion changes. Firstly, experimental protocols employing constant infusion of inulin with bladder washing, multiple control and test periods, and proof of constancy of plasma composition are more reliable than studies lacking one or more of these elements. Secondly, where plasma composition changes, possible effects of this change on excretion must be considered and thirdly, data obtained in the presence of rapidly changing states are less reliable than data obtained when filtration rate, urine flow and plasma composition are changing slowly. On the basis of these criteria Wesson (1957) concluded that filtration rate regularly changes in the presence of acute changes in sodium chloride excretion with only a few specific exceptions such as in osmotic diuresis. Whilst changes in filtration rate as a loading factor are a sufficient cause of observed changes in sodium chloride excretion this does not imply that changes in tubular reabsorbtive capacity do not contribute to the effects of load change, but it does mean that until experimental methods are refined there is no justification in unnecessarily postulating changes in reabsorbtive capacity. Experimentally it has been possible, in so far as the gross inaccuracies of clearance measurements will permit, to draw a correlation between changes in glomerular filtration rate and changes in the rate of sodium excretion (O'Connor, 1962).

A similar conclusion was reached by Selkurt (1954) who thought there was a possibility that small alterations in glomerular filtration rate, undetectable by clearance techniques might account for changes in urinary sodium excretion often considered significant in certain experiments of an acute nature. As a corollary it seems unwarranted to conclude that whenever an alteration in urine sodium occurs in the absence of detectable changes in glomerular filtration rate that a change in endocrine regulation (pituitary or adrenal) is the necessary alternative without more intensive investigation to prove the claim. As Dicker (1956) points out there is little harm in accepting the postulate that inulin is excreted solely by filtration provided it is considered as a working hypothesis rather than a revealed truth.

These views are not, however, universally held and Strauss (1957) noting the difficulties of interpretation of inulin and endogenous creatinine clearances concluded that until techniques are devised which can measure filtration rate with very great precision results in which changes in sodium excretion occur without significant changes in clearance values must be considered to represent altered reabsorbtion of sodium. It is believed that this is a very important difference of opinion which has led to many instances in which small changes in urinary excretion have been explained in terms of altered tubular function. It is better that such changes should remain unexplained rather than that a mechanism should be postulated for which there is no evidence.

In the discussion of experimental results which follows unless a certain exclusion can be made of minor changes in the filtered load, as a determinant of changes in the rate of excretion of salt, other mechanisms will not be postulated.

C. THE EFFECTS OF INFUSION.

The renal effects of any intravenous infusion depend upon the electrolyte composition and protein content of the infusate and upon the volume and rate of infusion. The effects vary according to the state of hydration and salt balance of the recipient.

Infusions of sodium chloride solutions have a uniformly constant effect in producing a prompt rise in the urinary excretion of sodium and chloride. This is an old observation and as Knowlton (1911) pointed out the more obvious changes which would be produced by dilution of the blood with physiological saline solutions are changes in the osmotic pressure of the plasma protein and changes in the viscosity of the blood. Starling (1899) showed that the available pressure in the glomerular capillaries for the filtration of urine is the difference between the capillary hydrostatic pressure and the osmotic pressure of the plasma proteins. The increase in net filtering pressure will lead to protein-free fluid leaving the plasma not only in the kidneys but also in other parts of the peripheral circulation. The assumption of a causal relationship between the lowering of colloid osmotic pressure and the diuresis following infusion of saline was supported by the lack

of a similar diuretic response to intravenous injection of gelatine or gum acacia in saline solution (Knowlton, 1911). In the isolated kidney Starling & Verney (1925) were able to show that urine flow stopped when perfusion pressure was lowered to about 40 mm Hg, but this limiting pressure could be lowered by diluting the serum colloids with normal saline.

Studies of infusion of isotonic solutions into dogs have been reviewed by Wesson (1957); such infusions consistently lead to a prompt rise in the urinary excretion of sodium and chloride and measurements made overwhelmingly support the view that this saline diuresis is attributable to an increase in glomerular filtration rate. Whilst infusions of saline invariably increase the excretion of sodium and chloride, the extent and characteristics of the increase may present various patterns under different circumstances (O'Connor, 1962). In the unanaesthetized dog maintained on a normal diet and without prehydration intravenous infusion of 100 - 250 ml. saline increased sodium excretion with little change in urine flow so that urine sodium concentration was increased (O'Connor, 1958a). If the dog was given priming doses of 300 ml. saline on the day before the experiment and a further 200 ml. four hours before the test then a different pattern was seen (O'Connor, 1955). The initial rate of sodium excretion was higher and increased markedly when saline was infused; this time however urine volume increased whilst there was little change in urine sodium concentration. In about one third of these experiments urine volume increased rapidly to reach 3 - 4 ml./min 30 - 40 minutes after the test dose, but the rise in sodium

excretion occurred more slowly reaching its peak after 60-70 min so that initially sodium concentration fell. Thus the initial polyuria showed characteristics similar to a brief water diuresis and was in fact inhibited by small doses of vasopressin. It is not possible to state however what mechanism is involved in the production of this diuresis; it could conceivably be due to dilution of circulating vasopressin; to inhibition of the release of vasopressin, or may represent a pattern imposed by the kidney when a sudden change in glomerular filtration occurs at a time when the kidney is being affected by only a minimal concentration of circulating vasopressin. In all these experiments the rate of excretion of sodium rose progressively to a maximum at the end of the infusion and fell as soon as the infusion ended. In all experiments the time course of the changes in the urinary excretion of sodium followed closely the dilution of the plasma solids.

In anaesthetized dogz also infusion of saline causes an increase in glomerular filtration rate (Young, Pearce & Stevenson, 1955). When a hyperoncotic solution of dextran was infused there was a brisk diuresis but no increase in inulin clearance was found in spite of the blood volume being increased by as much as 200%. However, their figures do show increases in renal blood flow and as urinary osmotic pressure was not measured the possibility that some dextran may have been excreted by the kidney cannot be excluded. No diuresis occurred in these experiments when blood or plasma was infused.

Pearce (1959) extended these observations and using dogs

anaesthetized with chloralose collected urine from the bladder. Infusions of 25% of the estimated blood volume of either Ringer-Locke solution or 6% bovine albumin in Ringer-Locke were given. These infusions resulted in a transient increase in urine volume during which there was little change in chloride concentration so that chloride excretion increased. Cutting the vagus nerves usually caused a transient reduction in urine flow followed by a slight increase during the hour after vagotomy, but did not alter the diuretic and chloruetic response to infusion. Where vagotomy was combined with carotid sinus denervation complete anuria sometimes occurred but in dogs in which urine flow was maintained infusion still caused diuresis. Atkins & Pearce (1959) measured exogenous creatinine and para-amino-hippurate clearances whilst infusing dog plasma or 6% bovine albumin solutions. Infusion caused a similar transient diuresis accompanied by an increased sodium excretion with both solutions, and neither vagotomy nor adrenalectomy prevented this response. No consistent changes occurred in either creatinine or para-amino-hippurate clearances but no significance can be attached to these measurements made at such small and rapidly changing rates of urine flow. No measurements were made of plasma concentrations of electrolytes. Pearce (1959) suggested that since the diuresis described in these experiments cannot depend upon stimulation of atrial receptors there must be 'volume receptors' in some other part of the circulation. There is however no necessity to postulate any mechanisms other than an increase in glomerular

filtration to account for these results.

An example of experiments which purport to show on inadequate evidence that infusions can provoke a diminished release of antidiuretic hormone are those of Zuidema, Clark, Reeves, Gauer & Henry (1956). Infusions of saline, isooncotic albumin solutions and dog plasma of between 10 - 20% of the calculated blood volume all caused an increase in urine flow from a preinfusion level of 0.2 - 0.4 ml./min to about 1 ml./min. Infusion of dog blood caused an increase in urine flow in 18 out of 26 dogs. Haemorrhage of 10 - 30% of the blood volume caused a fall in urine flow from a mean of 0.96 ml./min to 0.27 ml./min; the reason why the basal flow in these animals was so high is not clear. Two dogs that produced diuresis after infusion showed no urinary antidiuretic activity whilst in one in which there was oliguria after infusion there was increased antidiuretic activity in the urine. This antidiuretic activity was not identified as of neurohypophysial origin and no evidence is provided by these experiments which supports the hypothesis that the observed changes in urine flow were necessarily the result of alterations in the rate of release of anti-diuretic hormone from the neurohypophysis.

When human subjects ingest an increased quantity of salt and water the immediate increases in sodium chloride excretion are seldom as large as in the dog (Wesson 1957). However, human subjects are generally intolerant of large doses of sodium chloride by mouth but if intravenous infusions are given or a large dose

(more than 1 l.saline) can be taken by mouth then the effects are more definite (O'Connor, 1962). Both Wesson (1957) and Strauss (1957) have reviewed the effects of infusion in human subjects and only those studies frequently quoted as providing evidence in support of a theory of 'volume receptors' will be considered here.

The first demonstration that a 'water type' diuresis may follow ingestion of saline was made by Priestley (1916) and although Priestley's 'mixed salt' solution may have been slightly hypotonic (Strauss, 1957) this finding has been confirmed many times, the brief diuresis being similar to the one already described in dogs. Strauss, Davies, Rosenbaum & Rossmeisl (1951) infused 3 l.saline into recumbent human subjects and observed an immediate increase in urine flow. Excretion of sodium increased but more slowly than water excretion so that at first the urine became dilute. The greatest increase in sodium excretion occurred in those subjects with the highest initial level of sodium excretion. When the subjects were sitting the rates of urine flow and sodium excretion were comparatively low and when these subjects were infused only a small increase occurred. If these subjects then lay down there was an increase in urine flow and in sodium excretion but once again sodium excretion lagged behind urine flow and the urine at first became dilute. The change from sitting to the lying position is of course accompanied by various haemodynamic and urinary changes even without pre-infusion. Because endogenous creatinine clearances

did not change the authors postulate that the urinary changes were the result of altered tubular function but clearance measurements cannot be relied upon under these experimental conditions and there are no grounds for postulating altered tubular function. Crawford & Ludemann (1951) studied the effect on sodium excretion of infusing 1-3 l.saline into recumbent human subjects and at the same time made measurements of inulin clearance. The subjects were prehydrated with a litre of water the evening before the experiment. Urine flow and sodium excretion increased by only a small amount although sodium excretion increased more markedly in four subjects who had been maintained on a high salt diet and whose initial spdium excretion was higher than that of the subjects on a normal diet. In view of the small changes in sodium excretion and as no figures of plasma concentrations are available no conclusions can be drawn from the absence of any consistent change in inulin clearance. Ladd (1951, a & b) measured sodium excretion and inulin clearance (with bladder washout) in recumbent subjects at first non-hydrated and then after hydration with a loading dose of 2 l.water 8 - 13 hours before the test. The average initial sodium excretion and inulin clearance was greater in the subjects in the hydrated group. When 3 l.of saline was infused at 45-65 ml./min sodium excretion and inulin clearance increased in all subjects. In the prehydrated subjects inulin clearance reached its peak after 60 min from the start of the infusion and sodium excretion increased from 0.28 to 1.8 m-equiv/min. In the non-hydrated subjects inulin clearance

rose rather more slowly (peak at 75 min) and sodium excretion rose from 0.058 to 0.42 m-equiv/min. Thus the greatest increase in sodium excretion occurred when the initial rate of sodium excretion was already raised; this is similar to the effect seen in dogs (O'Connor, 1962). Wiggins, Manry, Lyons & Pitts (1951) found that when either saline or a 'balanced salt' solution was infused rapidly plasma protein concentration fell. Their measurements of inulin clearance showed no change but Wesson (1957) has questioned whether a steady state with respect to inulin distribution or clearance had been reached as there were sharp changes in clearance values during the control periods.

Bojesen (1954) used a method of estimating inulin clearance which he claimed was suitable for use during short periods and when urine flow was changing. He found the rates of excretion of water and chloride following saline infusion reached their maximum values soon after infusion and these coincided with the lowest plasma protein concentration. Thereafter the excretion of these substances varied inversely with the rising plasma protein concentration. Inulin clearance also increased but tended to lag behind the increases in chloride and water excretion. When plasma protein was added to the saline solution to provide a colloid osmotic pressure similar to that of the recipients plasma then infusion caused no immediate change in water and salt excretion although later there was a small increase in the excretion of these substances.

The effects of infusion of whole blood, plasma or human serum albumin have been extensively studied but with conflicting results (Wesson 1957). Smith (1951) reviewing the effects of infusion of plasma or human serum albumin thought it likely that effects on renal haemodynamics could account for most of the observed changes. The studies of Welt & Orloff (1951) have caused especial interest and have been quoted as supporting the theory of volume receptors. These workers infused 2 l.of a 4-6% solution of human serum albumin in saline into non-hydrated subjects and produced a diuresis of hypotonic urine accompanied by a small increase in sodium and chloride excretion. In the control study when 2 l.of saline was infused, the peak urine flow developed later but the total output of sodium and water was little different. Filtration rate estimated as endogenous creatinine clearance with voluntary voiding of urine showed no significant changes, but these measurements could not be expected to detect small changes in filtration rate. When a hyperoncotic solution of 25% albumin was infused in these subjects there was little effect on urine flow or sodium excretion. Other workers have found such solutions decrease sodium excretion (Goodyear, Peterson & Relman, 1949) and if infused during maximal water diuresis or in subjects with diabetes insipidus they cause a decrease in water excretion (Petersdorf & Welt, 1953). Thus although hyperoncotic solutions increase plasma volume they may cause a decrease in renal excretion of salt and water.

D. THE EFFECTS OF HAEMORRHAGE.

Haemorrhage of sufficient severity to produce hypotension and shock has profound effects upon the kidney and may eventually cause renal failure. Experiments by several workers (reviewed by Smith, 1951 p.762-766) have shown that when blood pressure falls to below 60-100 mm Hg in dogs there is a complete cessation of urine formation. These disturbances in renal function make impossible the estimation of renal blood flow by clearance methods. Selkurt (1946) measured renal blood flow directly by collecting from the renal veins and compared this with clearance estimations. Bleeding until mean arterial pressure was 60 mm Hg decreased renal blood flow to 41.5% of the control value whilst bleeding to 40 mm Hg pressure decreased renal blood flow to 11% of the control. The renal vascular resistance increased so that instead of 20% of the cardiac output flowing through the kidneys only 5% took this route. Following the acute fall in blood pressure there was often anuria so that clearance values fell to zero although there was still an appreciable blood flow through the kidneys. On reinfusion clearance values failed to rise as rapidly as renal blood flow and were of no value in the estimation of renal function.

The normally small renal arteriovenous oxygen difference remains small in early haemorrhagic shock despite the marked decrease in renal blood flow (Dole, Emerson, Phillips, Hamilton & Van Slyke, 1946). These findings contrast with those from the rest of the body where oxygen extraction increases and suggest a decrease in oxygen consumption by the kidney. Observations on human subjects suffering from shock as a result of injury

suggest that similar changes may be anticipated (Lauson, Bradley & Cournand, 1944). These investigators estimated glomerular filtration and renal plasma flow by inulin and para-amino-hippurate clearances in patients between 2 and 10 hrs after injury. Both clearance measurements were reduced to a greater extent than was expected from the arterial pressure fall suggesting active renal vasoconstriction and a reduced proportion of the cardiac ouput flowing through the kidneys. Whilst the limitations of measurements in these traumatized subjects with low urine flows are great they nevertheless indicate significant renal vasoconstriction in shock.

Observations of the effects of less severe haemorrhage have failed to show any definite response of the kidney to such a reduction of blood volume. The withdrawal of a small volume of arterial blood (5-10 ml./kg) from conscious dogs in which the kidneys were denervated, the splanchnic nerves sectioned and the abdominal sympathetic chains excised, caused a long lasting inhibition of water diuresis which has been attributed to release of antidiuretic hormone (Rydin & Verney, 1937), although this has never been verified. O'Connor (1962) was unable to produce inhibition of water diuresis when similar amounts of blood were withdrawn from the external jugular veins of dogs with an intact sympathetic system.

In dogs anaesthetized with chloralose removal of 10 - 30% of the blood volume induces oliguria (Zuidema, Clark, Reeves, Gauer & Henry, 1956). There was said to be no change in mean arterial pressure in these experiments although Henry, Gauer &

Sieker (1956) reported falls in arterial pressure of 5-10 mmHg in another series of experiments under entirely similar conditions. The urine of the majority of these dogs showed antidiuretic activity when tested on rats but no conclusions can be drawn regarding the nature of the antidiuretic activity or the agent acting on the kidney to cause antidiuresis.

In human subjects Brun, Knudsen & Raaschou (1945d) venesected 275 - 450 ml. of blood without any effect on urine flow. Similarly Lewis (1953) after applying venous occlusion cuffs to the thighs removed 500 ml. blood from a subject undergoing maximal water diuresis without causing any reduction in the rate of urine flow; the estimated fall in effective blood volume in this subject was 1200 ml. Lombardo, Eisenberg, Oliver, Viar, Eddleman & Harrison (1951) reported antidiuresis and a fall in sodium excretion when they removed 2.5 ml./kg from sitting subjects or 9 ml./kg from lying subjects; these were the largest volumes that could be removed without causing syncope. The changes in sodium excretion were in fact small and extremely variable. Plasma concentrations were not estimated and the failure to detect any change in endogenous creatinine clearance does not exclude the possibility that the observed urinary changes were due to changes in filtration.

Noble & Taylor (1953) estimated the antidiuretic activity in human urine using rats. Between 350 and 1270 ml. of blood was removed from an arm vein in about half an hour; some subjects fainted as a result of either the venesection or venepuncture and the urine subsequently voided always contained an antidiuretic

substance. The subjects who did not faint showed no increase in antidiuretic activity in the urine after venesection.

E. THE EFFECTS OF ORTHOSTASIS AND VENOUS OCCLUSION.

When the circulation is impaired by obstruction of a major venous drainage system or sequestration of the effective blood volume in the limbs as occurs in the passive erect posture, sodium excretion and creatinine clearance generally decrease and increase again when the circulation is restored. Movements of the two terms are essentially simultaneous and of roughly proportional magnitude and denervated kidneys respond similarly but less markedly than intact kidneys (Wesson, 1957).

A list of the early work on the effects of posture on renal function is given by Epstein, Goodyear, Lawrason & Relman (1951) and Brun, Knudsen & Raaschou (1945,a). The work of the latter authors is frequently quoted in connection with the theory of volume receptors. Their subjects were recumbent for 4 - 6 hours during which time they were loaded with water by drinking 100-200 ml. water every ten minutes; urine was collected either from the bladder or by voluntary voiding every 15 or 30 min. Clearance values were estimated using a single injection technique of inulin and per-abrodil (diodrast). After two or three control periods the subjects were tilted to 60°; in a typical experiment urine flow began to fall after about 15 min and in the course of an hour fell about 30%, when the subject was returned to the horizontal the urine flow immediately began to rise but only reached its

initial value gradually over the course of an hour. Accompanying the fall in urine flow there was a small fall in inulin clearance and the urine specific gravity increased. When the passive erect posture (60°) was maintained for one hour glomerular filtration was estimated to fall 20% and at the same time plasma protein concentration increased by about 10% (Brun, Knudsen & Raaschou, 1945,b), in these experiments arterial pressure was maintsined and mean arterial pressure sometimes increased as a result of an increased diastolic pressure. However, in some subjects if the passive erect posture is maintained syncope occurs as a result of circulatory collapse (Brun, Knudsen & Raaschou, 1945,c). When syncope occurred blood pressure fell and the heart rate slowed, the subject was immediately tilted back to the horizontal and pulse rate and blood pressure were immediately restored. In spite of the restoration of these cardiovascular parameters urine flow fell to relatively low levels (less than 2 ml./min) where it remained for 15-90 min. During this time plasma protein concentration fell markedly as a result of the dilution produced by the constant intake of water. A similar reduction of urine flow was seen in non-water loaded subjects who fainted although the magnitude of the change was less. About 200-450 ml. of blood was withdrawn from the water loaded subjects five minutes after collapse and infused into similarly water loaded recumbent subjects. In three experiments there was an inhibition of the water diuresis in the recipients (Brun, Knudsen & Raaschou, 1945,d). Urine chloride concentration increased during post-syncopal oliguria but chloride excretion usually fell

although plasma chloride concentration remained constant. In two patients with moderate diabetes insipidus post-syncopal oliguria was less marked and of shorter duration. These results indicate that the antidiuretic effect of the passive erect posture is due to changes in renal blood flow and an increase in plasma protein concentration; if syncope occurs there is probably a sudden release of sympathetic vasoconstrictor substances and of antidiuretic hormone from the neurohypophysis.

The fall in sodium and water excretion and reduction of glomerular filtration rate that accompanies the passive erect posture has been observed many times (Epstein, Goodyear, Lawrason & Kelman, 1951; Netravisesh, 1953), but these studies have all been made on subjects hydrated by ingestion of water or weak sodium chloride solutions. The experiments of Pearce & Newman (1954) are often said to provide evidence for the release of antidiuretic hormone in the erect posture. Their subjects were hydrated and tilted to 60° but were allowed to move their legs to prevent syncope; there was a fall in urine flow, sodium excretion and creatinine clearance. In other experiments alcohol was given 20 min before and immediately after tilting; alcohol inhibits the release of antidiuretic hormone from the neurohypophysis (van Dyke & Ames, 1951); the fall in urine volume was said to be less than in the experiments without alcohol although there was still a fall in the excretion of electrolytes. This fall was maintained even after the supine position was restored. Since alcohol was first given only 20 min before tilting there are no measurements to provide a pre-tilt control for these experiments

and it is seen from the results that the urine flow was still rising when the tilt was applied. In a control experiment alcohol was given but no tilt applied; there was at first an increase in urine flow followed later by a fall in urine flow and reduced excretion of electrolytes. These effects of alcohol administration appear to have been merely superimposed upon the effects of tilting and the experiments provide no evidence suggesting the release of antidiuretic hormone in the erect posture when syncope does not occur.

Epstein, Goodyear, Lawrason & Relman (1951) tried to counteract the effects of quiet standing by simultaneously expanding plasma volume with an intravenous infusion of 4% human serum albumin. Although they prevented the fall in plasma volume there was still a fall in urine flow and sodium excretion. Plasma protein concentration was not measured but it is likely that this would increase since protein free fluid would still be lost from the cardiovascular system and in fact the rateof loss might be increased by the additional volume.

In fully water loaded subjects sodium excretion and creatinine clearance decrease in the passive erect posture but there may be relatively small changes in urine volume (Surtshin & White, 1956).

The reverse of these effects, that is an increased excretion of water and sodium is seen in normally hydrated subjects changing from an erect to a supine posture; Thomas (1957) found these changes persisted for several hours. In similarly hydrated subjects Currie & Ullmann (1961) observed an increase in urine flow with little change in urine concentration began about 1-2 hrs after

lying down, this increase was transient and usually decreased after about an hour.

Hulet & Smith (1961) examined the effects of lying down in hydropenic subjects. After being ambulant for about 2 hrs their subjects lay down; after about 15-30 min there was an increase in urine flow with little change in osmotic concentration although sodium concentration did increase. These changes were sometimes transient but sometimes urine flow was still increasing after 90 min. The changes were not in any way affected by intramuscular injection of 10 units of vasopressin. Because of the low rates of urine flow no attempts were made to estimate filtration rates by clearance methods. However, detailed calculations of osmolar and free water clearance were made and indicated that in hydropenic subjects the diuresis was attributable primarily to increased excretion of sodium. It was postulated that urine osmotic pressure would remain constant in the face of increasing urine flow provided the rate of influx of solute free water into the medulla did not exceed a critical value. When the rate of influx is increased greatly as in osmotic diuresis the rate of removal of solute free water attains an approximately constant maximal value and the urine becomes more dilute.

A similar redistribution of blood may be brought about by compressing the thighs of recumbent subjects with cuffs inflated to a pressure about equal to arterial diastolic pressure. As discussed in a previous section this procedure reduces effective blood volume and causes a loss of a mainly protein free fluid

from the blood, thus blood leaving the occluded limb will have a high plasma protein concentration. In fact Landis, Jonas, Angevine & Erb (1932) found that with cuffs inflated to 80 mm Hg there could be a loss of as much as 19 ml. of fluid from 100 ml. of blood. After 30 min occlusion plasma protein concentration had increased by about 1.5 g/100 ml. This is a smaller increase than would be expected from the estimated loss of fluid and they suggest that at these high pressures some protein may also be lost. When lower pressures (60 mm Hg) were used there was no loss of protein but fluid was still lost and plasma protein concentration rose by 1 g/100 ml. Even with cuff pressures as low as 20 mm Hg there was some loss of fluid from the plasma. Levitt, Turner & Sweet (1952) applied tourniquets inflated to 10 mm Hg below diastolic pressure and found similar changes in plasma protein concentration although they noted a peak was reached after 1-2 hrs, after which time the concentration decreased. Sodium excretion and creatinine clearance both decreased as the plasma protein concentration increased.

Wilkins, Tinsley, Culbertson, Burrows, Judson & Burnett (1953) studied the effects of venous occlusion on sodium and chloride excretion and inulin clearance in normal and hypertensive subjects. Their subjects drank 200 ml. water every half-hour and at the time the tourniquets were inflated urine flow had reached about 6 ml./min but was still increasing. The cuffs were inflated to 70 mm Hg; after about 10 min, urine flow, sodium excretion, inulin clearance and para-amino-hippurate clearance began to decrease

whilst the concentration of sodium in the urine increased. When after about 30 min the cuffs were released there was often a further fall in urine flow and sodium excretion before these values began to rise again. Plasma protein concentration increased whilst the cuffs were inflated and often increased suddenly when the cuffs were released. There was no difference between the response in normotensive, hypertensive and sympathectomized hypertensive subjects. Fitzhugh, McWhorter, Estes, Warren and Merrill (1953) made similar inflations of cuffs in normal subjects and found the cardiac index fell by 20%. Urine flow and sodium excretion reached their lowest levels in the first post-inflation period although inulin and para-amino-hippurate clearance had already begun to rise.

In these experiments and many similar ones changes in sodium excretion often parallel changes in inulin clearance. However, the changes in clearance often appear either disproportionately large or disproportionately small when compared with the changes in sodium excretion. There is also a marked tendency in longer experiments for the maximal rate of change of inulin clearance to precede the period of maximal change of sodium excretion. If these changes are accepted uncritically a change in tubular reabsorbtive capacity may be suggested. However, it seems more reasonable to attribute excessive variations in inulin clearance to artefacts associated with the low and changing rates of urine flow in these experiments (Wesson, 1957). In general the observed changes in inulin clearance are more than sufficient to

account for the changes in sodium excretion

F. THE EFFECTS OF POSITIVE AND NEGATIVE PRESSURE BREATHING.

Breathing from a reservoir containing air at a pressure higher than atmospheric pressure leads to impairment of the circulation, some effects of which have already been discussed. Henry, Jacobs, Meehan, & Karstens (1948) found that during positive pressure breathing at a pressure sufficient to raise peripheral venous pressure to 40 mm Hg, a volume of fluid equivalent to 8% of the total blood volume could be lost from the circulation within 30 min. During respiration against a continuous pressure of 10-40 mm Hg urine flow is reduced (Drury, Henry & Goodman, 1947). Knoefel, Handley & Huggins (1953) examined renal function in anaesthetized dogs during positive pressure breathing at 9-31 mm Hg pressure. Blood pressure and cardiac output fell immediately on starting positive pressure breathing but gradually rose again; the renal response did not develop until about twenty minutes later. In half of the dogs there was antidiuresis and a marked reduction in sodium excretion; inulin and creatinine clearance were also reduced. These changes were present although smaller in a denervated kidney and were still present after vagotomy. In the other half of their experiments there was little change in urine volume, sodium excretion or creatinine clearance, but the maxmimal tubular reabsorbtion of glucose was increased and the authors suggested that this indicated that not all the nephrons had been functioning during the control periods. The antidiuresis and reduction in

sodium excretion can be readily accounted for by a change in renal blood flow and by the increased plasma protein concentration.

Breathing from a reservoir at a pressure less than atmospheric (negative pressure breathing) causes a small increase in urine flow in man and anaesthetized dogs. Gauer, Henry, Sieker & Wendt (1954) subjected dogs premedicated with morphine (0.7-1 mg/kg) and anaesthetized with chloralose to breathing from a reservoir at a pressure of -5 or -8 cm water. This led to a gradual increase in urine flow which reached a peak after 30-40 min and then decreased even when negative pressure breathing was maintained. The average change in urine flow was from 0.44 ml./min to 0.99 ml/min and examination of the results shows that in over half of the experiments the increase in urine flow was less than 100% of the control flow. Urine flow usually fell when negative pressure breathing was stopped but frequently remained at a level higher than before the manoeuvre and on occasions even continued to increase. No other renal parameter was measured. The diuretic response was abolished by cooling the vagus nerves in the neck to 3-4°c but was not affected by bilateral thoracic sympathectomy (Henry, Gauer, Sieker, Wendt, Reeves & Lee, 1953). More detailed studies were then made on conscious human subjects (Sieker, Gauer & Henry, 1954). The subjects were hydrated with a preliminary dose of 300 ml of 0.14% sodium chloride solution followed by 50 - 100 ml. of this solution every half hour. Urine samples were obtained by voluntary voiding and endogenous creatinine clearance measured.

After about 5 hrs urine flow became reasonably constant and after a further two hours when urine flow was between 1-2 ml./min negative pressure breathing was started. This led to a gradual increase in urine flow which reached its peak after 30 - 40 min when the average flow was 6 ml./min. There was no change in the excretion of sodium and potassium and urine pH remained constant. Endogenous creatinine clearance increased from a mean of 136 ml./min to 140 ml./min but no deductions can be drawn from these figures at these low and changing rates of urine flow.

Surtshin, Hoelzenbein & White (1955) repeated these experiments on anaesthetized dogs and on human subjects. In two dogs whose urine was collected for 5-6 hrs without negative pressure breathing, after stable rates of urine flow had been established, there were transient increases of 200% and 350% of the resting flows during which there was no change in sodium excretion. It is obvious from Fig.3 of their paper that in human subjects there were spontaneous variations in urine flow similar to the diuretic response to negative pressure breathing both in their time course and in the fact that there was little change in sodium excretion. However, in spite of these variations they were satisfied that in 'suitable' subjects negative pressure breathing does cause an increase in urine flow accompanied by only minor changes in sodium excretion. It was difficult to show any diuresis in dogs which had previously had the trigone of the bladder exteriorized and one kidney denervated, however, when there was a change in urine flow it appeared to affect both kidneys.

The effect of applying a fluctuating pressure to a reservoir from which subjects breathed has also been studied (Love, Roddie, Rosenweig & Shanks, 1957). They applied a pressure of plus or minus 20 mm Hg around a mean pressure of zero (atmospheric pressure), or 20 mm Hg, at a rate of 260 pulsations per minute. Their subjects received no prehydration and were studied after they had been lying for about 90 min at which time urine flow was usually falling after an initial increase. Pulsatile pressure breathing around a mean of either atmospheric pressure or 20 mm Hg pressure led to a small increase in urine flow but the variations in urine flow in the control periods both before and after the pressure breathing make assessment of its significance difficult. Osmolar concentration of the urine showed only small changes and sodium excretion increased although to a lesser extent than urine flow. Continuous positive pressure breathing at 20 mm Hg pressure caused no change in urine volume but as the resting flows in these experiments were less than 1 ml./min little further decrease could be expected. The authors postulated that the application of a pulsatile airway pressure should cause a greater discharge from intrathoracic receptors sensitive to stretch, than continuous negative pressure breathing. There is certainly no indication from their results that this somewhat startling procedure had more effect on urine flow.

Boylan & Antkowiak (1959) studied the effects of breathing from a reservoir at a pressure 15 cm water less than atmospheric.

Human subjects were hydrated by ingesting 50-150 ml. water every half hour, and voided voluntarily at intervals. Negative pressure breathing caused increasesin urine flow of between 45-262% in twelve of sixteen subjects. Sodium excretion, venous haematocrit and plasma osmolar concentration were unchanged. The experiments were then repeated after a loading dose of vasopressin 1 m-u./kg followed by an infusion of vasopressin 1 m-u./kg/hr. These subjects had very low urine flows (less than 1 ml./min) and urine was collected from an indwelling Foley catheter and the bladder emptied by rinsing, suprapubic pressure and air washout; they showed no diuretic response to negative pressure breathing. However, these subjects had a much lower sodium excretion than the normal subjects. It is unlikely that vasopressin in the doses given would reduce sodium excretion and it may be that other factors may have played a part in inhibiting urine flow and sodium excretion; in addition to the rather disturbing method of urine collection they were also receiving an intravenous infusion. In a third series of experiments when maximal water diuresis was induced there was no further increase in urine flow during negative pressure breathing. The authors interpreted their findings as providing indirect evidence that a reflex diuresis initiated by negative pressure breathing has its effect by inhibiting antidiuretic hormone secretion. In view of the anomalies mentioned this evidence is not entirely satisfactory.

Murdaugh, Sieker & Manfredi (1959) also using human subjects

found that continuous positive pressure breathing during water diuresis led to a reduction in urine flow. During alcohol diuresis positive pressure breathing was said to cause less antidiuresis. However, alcohol may effect the cardiovascular system in addition to the neurohypophys-ial release of antidiuretic hormone and in fact the clearance measurements indicate that effective renal plasma flow was about 20% higher during alcohol diuresis compared with that during water diuresis. It is therefore not possible to assess the significance of this finding. Negative pressure breathing was studied on subjects who received one glass (capacity not stated) of water every two hours. Negative pressure breathing caused a diuresis in eight of nine subjects during which there were only small changes in solute excretion. The administration of vasopressin was said to prevent the appearance of the diuresis but unfortunately no details of the dose used or the method of administration are given. The inadequate reporting of experimental details makes this paper worthless.

Hulet & Smith (1959) have made a careful study of the effects of negative pressure breathing in hydropenic normotensive subjects, hydropenic hypertensive subjects and normotensive subjects who had been prehydrated by water loading 8-9 hrs prior to the test. Prehydrated and hypertensive subjects are known to be particularly liable to respond to other stimuli with natriuresis. All three groups had basal urine flows of about 1.5 ml./min. The normotensive hydropenic and hypertensive subjects responded to negative pressure breathing with an increase in urine flow

accompanied by an increase in free water clearance in about half these subjects (average increase 1 - 1.5 ml./min). Small increases in sodium excretion in these subjects were attributed to a "washout" effect. The other half of the subjects showed either antidiuresis or an increase in urine flow accompanied by an increase in sodium excretion possibly attributable to an increase in filtration rate. In the group of prehydrated subjects seven out of ten subjects showed an increase in free water clearance and urine flow increased by an average of 2.4 ml/min with only small changes in sodium excretion. There were no changes in plasma osmotic concentration during negative pressure breathing. As the authors state it is clear that at best negative pressure breathing has a very mild diuretic effect. The changes in free water clearance were in fact statistically significant only in the prehydrated group, but in some subjects either prehydrated or hydropenic, negative pressure breathing does cause a small diuresis which cannot readily be accounted for in terms of agents known to act on the kidney.

The variability of the effects of negative pressure breathing is illustrated by the experiments of Baratz & Ingraham (1960) who were hoping to measure antidiuretic activity in the plasma during negative pressure breathing. They used dogs anaesthetized and otherwise treated similarly to those of previous investigators but were unable to produce a significant diuresis to examine. Jahn, Stephan & Stahl (1960) were unable to measure any antidiuretic activity in the urine or jugular venous blood of chloralose anaesthetized dogs either before, during or after negative pressure

breathing, although haemorrhage of about 25% of the blood volume increased the antidiuretic activity in the urine. They suggest that an active diuretic principle may be released during negative pressure breathing, but this theory would need to be investigated more fully before any conclusions could be made.

In man a small diuresis very similar in both time course and the excretion of solutes to that produced by negative pressure breathing accompanies other circumstances which alter respiration. Inhalation of 5-7% CO_2 by recumbent subjects leads to an increase in urine volume with no change in sodium excretion (Barbour, Bull, Evans, Hughes Jones & Logothetopoulos, 1953). Voluntary hyperventilation produced a similar diuresis but this was accompanied by an increased sodium excretion. Valtin, Wilson & Tenney (1959) also observed a diuresis when recumbent human subjects breathed 4.5 - 6% CO_2. This diuresis did not appear in the passive erect posture but did occur when the lower limbs were mildly exercised or when the subjects stood in water. Voluntary hyperventilation with air or 2% CO_2 caused a smaller diuresis accompanied by an increased sodium excretion. Cats anaesthetized with chloralose also showed a diuresis when breathing 6% CO2 and this still appeared and was sometimes even enhanced after the vagus nerves had been cut.

Ullmann (1961) has recently found similar urinary changes occurring in response to anoxia or hypocapnia. Breathing a mixture of 10-14% oxygen in nitrogen to produce anoxia with hypocapnia, or voluntary overbreathing, both led to an increased

urine flow; in dehydrated subjects the urine flow doubled (basal level 1 ml./min) and in hydrated subjects the response to water ingestion was enhanced. Both procedures were accompanied by an increase in solute excretion. When hypocapnia was prevented by the addition of carbon dioxide to the gas mixture then although there was an increase in water excretion solute excretion remained constant. The polyuria which accompanied manoeuvres such as forced breathing, breathing 5.5% CO_2 or 10% O_2 was transient and was not related to respiratory minute volume or to end-expiratory carbon dioxide concentration (Currie & Ullmann 1961). During their experiments it became obvious that breathing through a standard valve could cause polyuria even though respiratory rate did not change. Valve breathing increased the amplitude of intra-oesophageal pressure variation by about 10 mm Hg and produced a diuretic effect as great as that found when additional respiratory manoeuvres were used. Whilst these various manoeuvres do produce transient increases in urine flow it should be noted that the increases are usually less than 100% of the control values. No cardiovascular parameters were measured during these experiments.

G. CONCLUSIONS.

There is little doubt that haemorrhage severe enough to cause peripheral circulatory failure, or a less severe haemorrhage causing fainting will lead to an increased release of antidiuretic hormone from the neurohypophysis, in addition to renal vasoconstriction.

It is likely that such a release of antidiuretic hormone is similar to that associated with any painful stimulus or emotional stress (Rydin & Verney 1937; O'Connor & Verney 1942; O'Connor 1946). There is no evidence that bleeding causing a moderate reduction in blood volume has any effect on urine flow even during water diuresis. Most of the effects of haemorrhage on the urine can be accounted for by a reduction in glomerular filtration plus in some cases a release of antidiuretic hormone.

Infusions of saline and iso-oncotic solutions expand intrathoracic volume and cause an increased urine flow and sodium excretion. These effects are still seen after the vagus nerves are cut and are therefore unlikely to depend upon an increased discharge from intrathoracic receptors. Saline infusion causes dilution of plasma protein and both procedures may be accompanied by an increased glomerular filtration rate. When infusion is made into water or saline loaded dogs or humans the diuresis may at first resemble a water diuresis in that there may be an increase in water excretion with little change in sodium excretion and this diuresis may be inhibited with small doses of vasopressin. It may be that the circulating levels of endogenous antidiuretic hormone should be low for this effect to appear and there is no real evidence that the rate of release of antidiuretic hormone from the neurohypophysis is inhibited. Infusions of whole blood, in general, have remarkably little effect on urine flow in humans, and in dogs the results may be affected by transfusion

reactions involving the rapid loss of fluid and protein from the vessels. Expansion of the blood volume by infusion of hyperoncotic solutions although it distends the intrathoracic circulation usually decreases urinary excretion of sodium and water and also decreases glomerular filtration rate.

Standing in the passive erect posture causes pooling of blood in the lower limbs and a reduction in intrathoracic volume. At the same time plasma protein concentration gradually increases and there is also some vasomotor compensation for the loss of effective blood volume. Only when fainting occurs is there any evidence of increased release of antidiuretic hormone from the neurohypophysis. On lying down these effects are reversed and there is usually a transient increase in urine flow and sodium excretion; similar small changes in sodium excretion occur even when hydropenic subjects who have received a large dose of pituitary extract lie down. These changes can be accounted for by changes in glomerular filtration.

Positive pressure breathing reduces intrathoracic blood volume but also reduces cardiac output and causes an increase in plasma protein concentration. Urinary changes can only be fully accounted for in terms of reduced filtration. Negative pressure breathing and any other manoeuvres which increase pressure fluctuations in the chest may lead in prehydrated human subjects and anaesthetized dogs to a small diuresis; there is little change in solute excretion during this diuresis and the diuresis may be prevented in conscious human subjects by infusion of

vasopressin. In hydropenic subjects there may be smaller changes in urine flow, and sodium excretion may increase. Sieker, Gauer & Henry (1954) after examining the effects of negative pressure breathing concluded that whilst the exact manner in which such a stimulus led to a diuresis was uncertain, it must involve the central nervous system and the antidiuretic hormone of the posterior pituitary gland. This conclusion was based on the fact that the urinary sodium concentration fell during the diuresis and the diuresis did not start until about fifteen minutes after the negative pressure breathing began. They believed that the possibility of a direct cardiovascular effect upon the kidney causing the diuresis was eliminated as there was no change in heart rate or blood pressure in their human subjects. Their method of recording blood pressure did not allow this conclusion and cardiac output may increase during negative pressure breathing in human subjects (Kilburn & Sieker, 1960).

Thus most of the urinary changes associated with changes of intrathoracic blood volume (Table 1) can be explained by changes in glomerular filtration rate. There remains a small, transient diuresis sometimes seen after infusions of saline, on lying down, or with negative pressure breathing; during this diuresis the urine becomes more dilute. Each of these procedures causes an increase in intrathoracic blood volume or an increased discharge from intrathoracic receptors, but also has effects upon other parts of the circulation and may affect renal blood flow and glomerular filtration. The diuresis occurs only in well hydrated subjects

at rest or in chloralose anaesthetized animals. Decreased release of antidiuretic hormone would explain some of the features of this diuresis and in human subjects the diuresis is inhibited by the administration of vasopressin. It is likely that in those conscious human subjects in which the diuresis appears there is a low level of circulating antidiuretic hormone, so that if glomerular filtration were suddenly increased the urine might present the appearance of a small water diuresis. In fact these subjects frequently showed spontaneous variations in urine flow during which there was a fall in urine sodium concentration. (Surtshin, Hoelzenbein & White, 1955). In view of this even a valid demonstration that the polyuria is abolished by vasopressin does not prove that the immediate agent acting on the kidney is a decreased release of antidiuretic hormone, as infusion of vasopressin may change a necessary background state.

The diuretic response to negative pressure breathing and lying down cannot be accounted for in terms of known mechanisms, but it does not in itself provide sufficient evidence on which to base an unsupported theory of 'volume receptors'.

CHAPTER IV.

THE EFFECTS OF DISTENDING THE LEFT ATRIUM.

On the evidence so far presented other workers have reached the conclusion that the existence of 'volume receptors' was likely, and have searched for specific mechanisms. Henry, Gauer & Reeves (1956) suspected that the afferent mechanism by which negative pressure breathing caused diuresis was congestion of the intrathoracic circulation which would affect stretch receptors in the heart and lungs. They therefore made a series of experiments in an attempt to localize the site of the receptors; the effect on urine flow of obstructive distension of the left atrium, which increases pressures throughout the pulmonary vascular bed, was compared with the effect of closing snares around the pulmonary veins and the effect of producing pulmonary arterial hypertension by embolism of the pulmonary arterioles. A diuresis was elicited only by expansion of a balloon in the left atrium. In spite of the obstruction to the circulation caused by inflation of a balloon in the left atrium, systemic arterial pressure did not change significantly and in the great majority of tests there was a small increase in urine flow. This diuresis like that of negative pressure breathing began about ten minutes after the procedure started and lasted for about thirty minutes whether or not left atrial distension was maintained for a longer period. The authors believed that these results linked the stretch receptors in the left atrium and pulmonary veins with

homeostatic responses of the kidney as a mechanism reacting to changes in the actively circulating blood volume. Henry & Pearce (1956) showed that balloon inflation in the left atrium increased the discharge of impulses from atrial receptors. When these impulses were blocked by cooling the vagus nerves in the neck then the diuretic effect of balloon inflation was abolished.

This diuresis did closely resemble that produced by negative pressure breathing and thus once again a small diuresis was produced in chloralose anaesthetized dogs by a primarily cardiovascular change. Whilst Henry et al. (1956) believed that the diuresis of negative pressure breathing was the result of a diminished release of antidiuretic hormone they did not commit themselves to any statement as to the agent acting on the kidney in atrial distension. However, many other authors have accepted the idea that stimulation of stretch receptors in the left atrium would cause a diminished release of antidiuretic hormone (Smith, 1957; Grossman, 1957; Strauss, 1957; Neil, 1960), and more recently Pearce (1961) and Gauer, Henry & Sieker (1961) have developed this hypothesis.

Since inflation of a balloon in the left atrium appeared to provide the most controlled conditions for production of the diuresis, and at first sight seemed to give the most localized stimulus, it was decided to repeat the experiments of Henry, Gauer & Reeves (1956) and attempt by careful examination of cardiovascular and urinary changes to elucidate the mechanism producing the

diuresis. The results of these experiments appear in the next section.

PART II.

EXPERIMENTAL METHODS AND RESULTS.

In the experiments to be described two techniques were used. Firstly, the mitral orifice was blocked by a balloon, thus distending the left atrium and causing congestion of the whole pulmonary vascular bed; these experiments were a repetition of those of Henry, Gauer & Reeves (1956). Secondly the intrapericardial portions of the left pulmonary veins were distended without causing any obstruction to blood flow through the left atrium. Measurements of urinary and cardiovascular parameters were made during these procedures.

CHAPTER I.

THE EFFECTS OF OBSTRUCTING THE MITRAL ORIFICE IN ANAESTHETIZED DOGS.

A. METHODS.

I. ANAESTHETIC AND GENERAL MANAGEMENT.

The experiments were carried out following closely the methods described by Reeves, Henry & Gauer (1956). Young dogs of 10-15 kg were selected and fed on a diet of fresh meat and biscuits for two to eight days before the experiment. They received no food for 24 hours before the experiment but a plentiful supply of water was provided in their cages. All animals were given 15 mg morphine sulphate by subcutaneous injection and one hour later were anaesthetized by the slow intravenous infusion of a warm solution of chloralose 1% (British Drug Houses; 10 ml = 0.1g/kg) in sodium chloride solution 0.6g/100 ml. Usually no additional anaesthetic was needed during the surgical procedures which were normally completed in about 2½ hours. Occasionally some dogs were restless and developed pronounced reflex muscular twitching in which case a supplementary dose of anaesthetic was given. Subsequently during the experimental procedure a steady state of light anaesthesia was maintained by the infusion every ten minutes of either 1 or 0.5% chloralose, 1 ml./kg. It was usually found that if 0.5% chloralose was used the anaesthetic lightened whereas if 1% chloralose was given the animal gradually became more deeply anaesthetized. The anaesthesia was just enough to prevent muscular movements; the animal showed a

reflex jerk if the table was tapped and blood pressure and heart rate increased transiently, but the animal lay quietly if not stimulated. Variation in the level of anaesthesia could sometimes be seen over the ten minute periods between injections of anaesthetic. Immediately after an injection of chloralose the heart rate would slow and then gradually increase over the ten minutes until the next injection; such changes were of the order of 10 beats/min and were not seen when the heart rate was rapid.

The chloralose solution was prepared by dissolving 5g chloralose in 500 ml. of 0.6% sodium chloride solution and placing this in a water bath maintained at 65-75°C. The chloralose was kept at this temperature throughout the experiment and the bottle stoppered to prevent evaporation. Even at this temperature there was a tendency for the chloralose to come out of solution and each dose was filtered immediately before use.

2. SURGICAL PROCEDURES.

When the animal had been anaesthetized hair was shaved from the flanks, the chest and neck, and the skin washed. No sterile precautions were taken during the experiments but all instruments were sterilized between experiments. No antibiotics were given either before or during the experiments.

The trachea was cannulated and a six-inch long wide bore polyethylene tube attached to the cannula to compensate for the loss of dead space normally provided by the pharynx. In some experiments the vagus nerves were freed and loose ligatures placed around them to aid identification later.

Each ureter was approached through a muscle-splitting flank incision 1 cm above and parallel to the iliac crest. At first a retroperitoneal approach was used but it was found that this often led to bleeding from retroperitoneal vessels, buried in fat, that was difficult to control. By opening the peritoneal cavity the ureters could be immediately identified and were catheterized without significant blood loss. Polyethylene tubing of 1 mm bore was used to catheterize the ureters; the end of the tubing was filed down to avoid damaging the ureteric epithelium. Each catheter was inserted so that its tip lay at about the level of the lower pole of the kidney. The dead space in each catheter was then less than 1 ml. The incisions were closed in layers and the catheters brought out through the incisions. Urine was collected from each catheter into test tubes and its volume measured every ten minutes; the samples from the two sides were kept separately until chemical analysis had been made. Henry et al. (1956) collected urine from a urethral catheter.

In experiments in which one kidney was denervated the right kidney was approached through an incision 1 cm below and parallel to the 12th rib. All fascial connections were divided between ligatures until the only attachments of the kidney were the blood vessels and the ureter. Obvious nerve trunks were severed, the vessels stripped free of fascia and the ureter catheterized and divided below the catheter.

Positive pressure ventilation was provided from a Starling 'Ideal' pump and the stroke volume and rate of respiration adjusted to about equal that of the animal's spontaneous respiration.

A resistance to expiration of 2 cm water was provided to ensure adequate inflation of the lungs. Thoracotomy was performed in the left fifth intercostal space and bleeding carefully controlled by using blunt dissection, coagulating minor bleeding points and ligating larger vessels. The ribs were retracted and the lobes of the left lung carefully separated at the cleft between the cardiac and diaphragmatic lobes so that the pericardium was exposed. The pericardium was incised about 1 cm anterior and parallel to the phrenic nerve and bleeding points ligatured. The tip of the left atrial appendage was gripped with forceps and pulled up through the pericardial incision. A soft string snare was placed around the base of the appendage and tightened. The tip of the appendage was removed, the cut edges secured with forceps and a balloon inserted into the appendage, the snare was then loosened and the balloon pushed on into the atrium. A ligature around the tip of the appendage held the balloon in position. The atrial balloon was made from a 2 cm length of the finger of a surgical glove tied over the end of a polyethylene tube of 2 mm bore. A second polyethylene tube of 1 mm bore was tied alongside the balloon for the measurement of mean left atrial pressure. The balloon was judged to be satisfactorily placed when it lay with its base included in the ligature around the tip of the atrial appendage. The balloon was inflated at each test with enough 0.9% sodium chloride solution (usually about 1 ml./kg body weight) to cause a rise of left atrial pressure of about 20 cm water. A wide bore rubber drainage tube was inserted through a stab wound in the 7th intercostal space and secured with a ligature; it lay with its end in the paravertebral

gutter. The ribs were drawn firmly together with ligatures and the tubes from the atrium led out through the incision. A layer of paraffin gauze (Paranet, Vernon & Co.Ltd.) was laid over the intercostal space and the muscles closed in layers over this. A further layer of paraffin gauze was placed over the muscles and the skin closed with a continuous suture. The drainage tube was led to an underwater seal and air expelled from the chest by increasing the stroke of the respiratory pump for a short time. When no more air could be expelled the pump was disconnected and spontaneous respiration began almost immediately. The level of the water in the drainage tube gave an indication of the negative pressure in the chest, usually about 3-5 cm H_2O during the expiratory pause, and also gave warning of the presence of air in the chest on the one occasion when a leakage occurred. After completion of the operative procedures at least two hours were allowed to elapse before the first experimental tests. Rectal temperature was maintained between 37.5 and 38.5°C by adjusting heating lamps.

A wide bore metal cannula was placed in the left femoral artery for the recording of arterial blood pressure. A glass cannula was placed in the left femoral vein and anaesthetic solution was given through this and each dose washed in with 2 ml. 0.9% sodium chloride solution from a burette. A polyethylene tube (1 mm bore) was inserted into the right femoral vein and in some experiments used for recording pressure in the inferior vena cava. Femoral arterial pressure, mean left atrial pressure and inferior vena caval pressure were recorded by capacitance manometers

operating ink writers; the frequency response of the systems was limited by that of the ink writer which was flat (± 5%) to 20 c/s. The atmospheric zero for each manometer was recorded at frequent intervals and the manometers were calibrated against stepwise alterations in pressure on a water or mercury manometer. Atmospheric zero was compared with 'true' zero by recording the pressure at the cannula tip when this was free in air, post-mortem. This was done after cutting away the respective heart chambers and vessels and making sure no obstruction was caused by blood or other tissues. In some experiments respiration was recorded from a sensitive capacitance manometer connected to a cannula in the right pleural cavity or the trachea.

Vasopressin was infused through a cannula threaded through a femoral vein so that its tip lay in the inferior vena cava. A motor driven syringe delivered 0.14 ml./min of 0.9% sodium chloride solution throughout the experiment, when required vasopressin (Pitressin; Parke, Davis & Co. batch LZ1094C or LY258J) was added to give the stated rate of infusion. The batches of 'Pitressin' were labelled as containing 20 u./ml. of pressor activity; in this report 1 m-u means 0.00005 ml. of 'Pitressin'.

3. CHEMICAL ANALYSIS.

Urine was analysed for sodium and potassium using an E.E.L. flame photometer. The instrument was adjusted to read zero with distilled water and to give full scale deflection with a standard solution. The standard contained 2.9225 g/l.NaCl and 1.8637 g/l.KCl (0.05M NaCl, 0.025M KCl) and was diluted 100 times with distilled

water before use; thus full scale deflection was given with 0.0005M NaCl or 0.00025M KCl. As the scale reading was nonlinear with respect to concentration a calibration curve was prepared using solutions of NaCl and KCl of known concentration. Urine samples were diluted in distilled water in 100 ml. measuring flasks to give a scale reading between 20 - 80% of full scale. This usually meant using a dilution of 1 in 500 or 1 in 1000. Agreement of duplicate estimations on urine samples was to within ± 0.005M NaCl and ± 0.0025M KCl.

Ammonium concentration in the urine was estimated using the microdiffusion technique described by Conway (1957). This method involves the release of ammonia from the urine by the addition of alkali, the ammonia then being absorbed by boric acid. The pH of the boric acid is about 5.0 before absorbtion but rises to upwards of 8.0 when the ammonia is absorbed. It is then titrated back to pH 5.0 with hydrochloric acid. In the estimations described here 1% boric acid was used to which was added a mixture of bromocresol green and methylene blue as an indicator. This mixture was placed in the inner chamber of the Conway 'diffusion unit', 0.2 ml. of urine was placed in the outer chamber and 1 ml. of saturated potassium carbonate added. The unit was left 40 min for diffusion to take place and the contents of the central chamber then titrated with $^{N}/_{50}$ HCl from a Conway burette; the end point was a change from a blue-green to pink. These colours were pale and the end point could not be clearly seen in artificial light. All estimations were made within an hour of the urine being passed and duplicate estimations on the same urine samples agreed to within ± 0.002M ammonium.

The total solute concentration in the urine was estimated by determining the depression of the freezing point of water induced by the urine. The apparatus consisted of a lagged metal bath in which was placed a freezing mixture of crushed ice and salt. The temperature of this mixture was about $-5^{\circ}C$. The bath was covered by a lid through which projected a wide bore test-tube long enough to reach almost to the bottom of the bath. Into this test-tube was fitted a smaller inner tube in which the urine was placed along with a Beckmann thermometer and stirrer; about 10 ml. of fluid was required to completely cover the thermometer bulb. A standard Beckmann thermometer graduated to $0.01^{\circ}C$ was used; zero ($0^{\circ}C$) was set each day with distilled water and was checked between each set of estimations on the urine. To provide a large enough volume of fluid it was usually necessary to dilute the urine ten times with distilled water. The urine solution of this dilution usually depressed the freezing point by about $0.2^{\circ}C$. During periods of diuresis more urine was available and the urine was diluted less; estimations were occasionally repeated using the same dilution throughout. As the results turned out the use of a less dilute urine in estimations on samples taken during a diuresis meant that the depression of the freezing point was still about $0.2^{\circ}C$. The main difficulty encountered in estimations of the freezing point depression was the judging of the actual freezing point of the fluid. It was found that if the fluid under test was stirred vigorously throughout its cooling it would reach a temperature about $0.2^{\circ}C$ below its freezing point and then suddenly rise rapidly to a point at which the temperature remained steady for 1 - 2 minutes

before beginning to fall slowly again. The freezing point was taken to be the highest temperature reached when the temperature rose after supercooling. Using this technique duplicate estimations using either the same or different dilutions of urine gave agreement on urine solute concentration to within ± 5%. Undercooling introduces errors in the estimation of freezing point depression since the observed freezing point will be lower than the true value by a factor related to the degree of undercooling, the heat capacity of the solution, the heat of fusion of the solution and the specific heat of the mercury in the thermometer bulb. However, if an attempt was made to prevent undercooling this was not always successful and the results obtained were more variable. In these experiments the absolute osmolar concentration was of less interest than a comparison between the concentrations at different times. It was therefore felt that by using the same volumes of fluid in the one apparatus and by adjusting the dilution of the urine so that the depression of the freezing point was about the same in each estimation a more valid comparison of samples could be made. From the results so obtained the osmolar concentration of the samples was calculated using the assumption that with water as the solvent a solute concentration of 1 gramme molecule per litre produced a depression of the freezing point of 1.86°C (Bayliss, 1959). This relationship holds only for solutions of non-electrolytes and does not therefore give the true molecular concentration of the urine. However, it has become standard practice to use this method to allow comparison of the osmotic activity of body fluids and it was in this context that the estimations of this report were made.

The pH of the urine was determined approximately using indicator papers. These estimations were occasionally checked with a Radiometer P.H.M. 22 pH meter using standard glass and calomel electrodes; the indicator papers gave results to within ± 0.3 pH units of the reading of the pH meter.

Plasma glucose concentration was determined using an E.E.L. colorimeter and a modification of the method of Folin and Wu (1919) described by the makers of the instrument. Standard solutions were prepared by dissolving 100 mg pure anhydrous glucose in 0.3% benzoic acid solution made up to 100 ml. From this solution standards were made by dissolving 1, 2, 3 or 4 ml. of the standard solution in 100 ml. 0.3% benzoic acid (equivalent to 40, 80, 120 and 160 mg glucose/100 ml. plasma). Proteins were precipitated from 0.1 ml. plasma by adding 3.7 ml. isotonic sodium sulphate-copper sulphate solution and 0.2 ml. sodium tungstate solution and the mixture was then filtered; to 1 ml. of either this filtrate, or a standard, or a blank (1 ml. distilled water) was added 1 ml. of an alkaline copper reagent and the mixture was placed in a boiling water bath for 10 min. After cooling 3 ml. of a phosphomolybdic acid reagent and 5 ml. of water were added. The colorimeter was adjusted to read zero with the blank solution and using the standards a calibration curve was plotted. The values for the concentration of glucose in the plasma samples were read off in mg glucose/100 ml. plasma. Duplicate estimations on plasma samples agreed to within ± 4 mg Glucose/100 ml. plasma.

Solid content of the plasma was determined by weighing, drying

and reweighing about 0.3 ml. of plasma. The samples were dried at 95 - 105°C for 3 hours after which there was no further weight loss. Total solids in the plasma include about 0.9g/100g of sodium salts and 1g/100g of solids other than proteins (fats, lecithin etc.) (O'Connor, 1955). For comparison with plasma protein a simple adjustment is to subtract 2g/100g from the values of plasma solids.

B. RESULTS.

1. REPETITION OF THE EXPERIMENTS OF HENRY, GAUER & REEVES (1956).

The mitral orifice was obstructed by inflation of a balloon in the left atrium in thirtyone dogs. The results of the first three experiments will not be included as these experiments served to establish a routine for the operative procedure, administration of anaesthetic and measurements of blood pressure and urine flow. In some experiments the vagus nerves were cut, one kidney was denervated or an infusion of vasopressin was given, but to allow comparison with the results of Henry et al. (1956) these will be described separately. There remain twentyfour balloon inflations in eighteen dogs when no additional interference was made.

(a) CARDIOVASCULAR AND RESPIRATORY EFFECTS.

Inflation of a balloon in the left atrium caused an immediate increase in left atrial pressure; usually about 1 ml./kg body weight of saline in the balloon was sufficient to raise left atrial pressure by about 20 cm water. When about this volume had been injected a small increase or decrease in volume (about 1 ml.) would cause a large rise or fall in left atrial pressure of as much as 10 cm water. An attempt was therefore made to adjust the volume

Dog No.	Urine Flow ml./min			Art.B.P. mm Hg			L.A.P. cm H_2O			Heart Rate beats/min			Resp.Rate /min		
	B	D	A	B	D	A	B	D	A	B	D	A	B	D	A
4(a)	0.9	1.41	0.68	91	83	91				140	190	155	35	42	35
5(a)	0.18	1.89	0.8	111	104	125	7	37	7	75	160	95	24	42	24
(b)	0.47	1.77	0.42	120	104	116	17	40	17	90	150	100	24/min		
6(a)	1.18	2.12	1.1	110	95	100	8	29	11	115	145	150	36	40	38
(b)	0.78	0.42	0.48	90	75	90	7	37	16	170	190	180	44	50	55
7(a)	0.39	0.91	0.56	107	73	105	12	33	14	145	165	145	24	33	28
8(b)	0.19	0.25	0.11	101	102	110	12	35	10	85	180	90	10	17	13
9(a)	0.24	0.71	0.39	107	97	99	6	33	8	170	200	180	25	30	23
(c)	0.40	1.37	0.54	95	94	94	5	25	5	165	195	165	26	26	23
10(b)	0.19	0.11	0.21	120	108	120	3	25	3	200	200	200	24	26	24
11(a)	0.19	0.18	0.08	120	112	120	12	35	8	120	200	120	6	11	6
12(a)	2.28	3.34	1.36	122	118	107	7	18	7	200	200	210	28	30	28
(c)	0.39	0.73	0.45	115	107	112	7	19	7	200	210	180	33	36	36
13(a)	0.34	0.62	0.42	103	83	96	2	19	2	200	230	205	14	18	16
(c)	0.44	0.48	0.46	76	68	70	4	22	5	180	180	180	27	28	26
14(a)	0.23	1.11	0.54	100	90	102	0	22	2	230	230	220	21	30	23
(c)	0.29	1.51	0.39	103	85	100	0	22	0	215	215	220	25	30	23
20(a)	0.88	1.23	0.92	100	90	100	2	27		115	200	140	12	17	17
21(a)	0.10	0.30	0.14	115	102	115	3	25	5	120	240	180	43	65	50
22(a)	0.20	1.42	0.39	115	95	115	3	35	3	125	205	130	10	22	11
23(a)	0.15	0.51	0.24	104	103	105	5	30	6	170	235	200	17/min		
26(a)	0.24	1.30	0.43	117	112	117	6	19	5	110	170	100	18/min		
27(a)	0.05	0.12	0.04	150	132	140	10	25	10	180	240	235	18/min		
28(a)	0.19	1.79	0.63	93	87	83	5	35	6	90	145	125	18/min		
Means	0.41	0.91	0.42	108	97	106	6	28	7	150	194	163	21	31	26

Table 2. Results of twenty-four, half-hourly balloon inflations in eighteen dogs. Figures for blood pressure, heart rate and respiratory rate are the mean values for 40 min before inflation (B), 30 min during inflation (D) and 40 min after inflation (A). Figures for urine flow are for the 40 min before inflation (B), the last 20 min of inflation and the first 10 min after deflation (D) and the 40 min after this time (A).

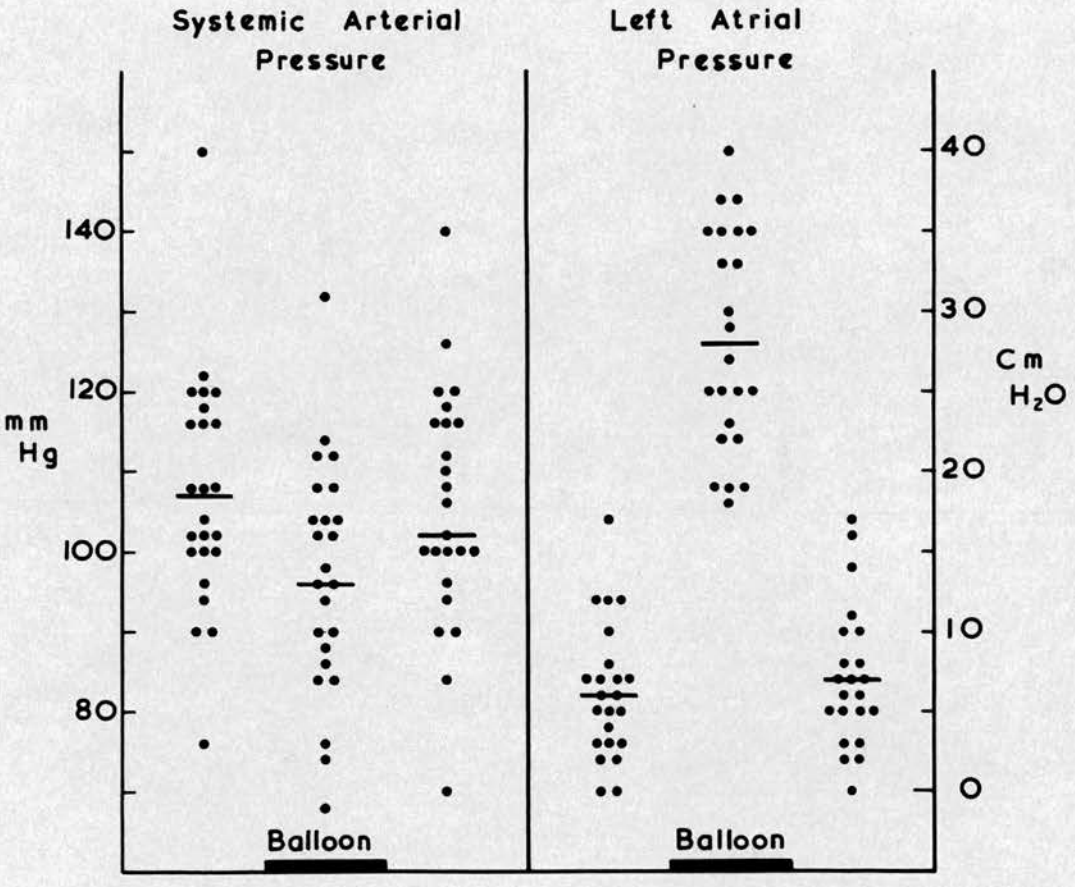

Fig.1. Changes in mean arterial pressure and mean left atrial pressure in twenty-four balloon inflations. Figures from Table 2. The horizontal lines represent mean values.

injected so that left atrial pressure increased by about 20 cm water. In practice there was an increase in left atrial pressure of between 11 and 32 cm water, from a mean of 6 cm water before inflation to a mean of 28 cm water during inflation; the individual changes are listed in Table 2. Once the pressure in the left atrium was established it remained constant whilst the balloon was inflated and fell promptly to about its previous level when the balloon was deflated. During balloon inflation the oscillations of the atrial pressure record greatly increased mainly as a result of mechanical interference with the flexible polyethylene catheter from which the pressure was recorded (Fig.2). However on some records it was apparent that some of the oscillation was due to a marked increase in pressure during atrial systole.

When a balloon was inflated in the left atrium systemic arterial pressure usually fell rapidly by between 10 - 40 mm Hg. However it recovered within 1-2 min to reach a level somewhat lower than the pressure before inflation. After deflation of the balloon arterial pressure rose to about its pre-inflation level. In Table 2 the mean pressure during inflation of the balloon is compared with the mean pressure for 40 min before and after inflation. The average fall in mean arterial pressure during balloon inflation was 10 mm Hg (S.E.M. $\pm$ 1.3) and ranged from 0 - 30 mm Hg; these changes are illustrated graphically in Fig.1. Henry et al. (1956) stated that there was no consistent change in systemic arterial pressure on balloon inflation and these figures have therefore been subjected to statistical analysis. The arterial pressure during balloon

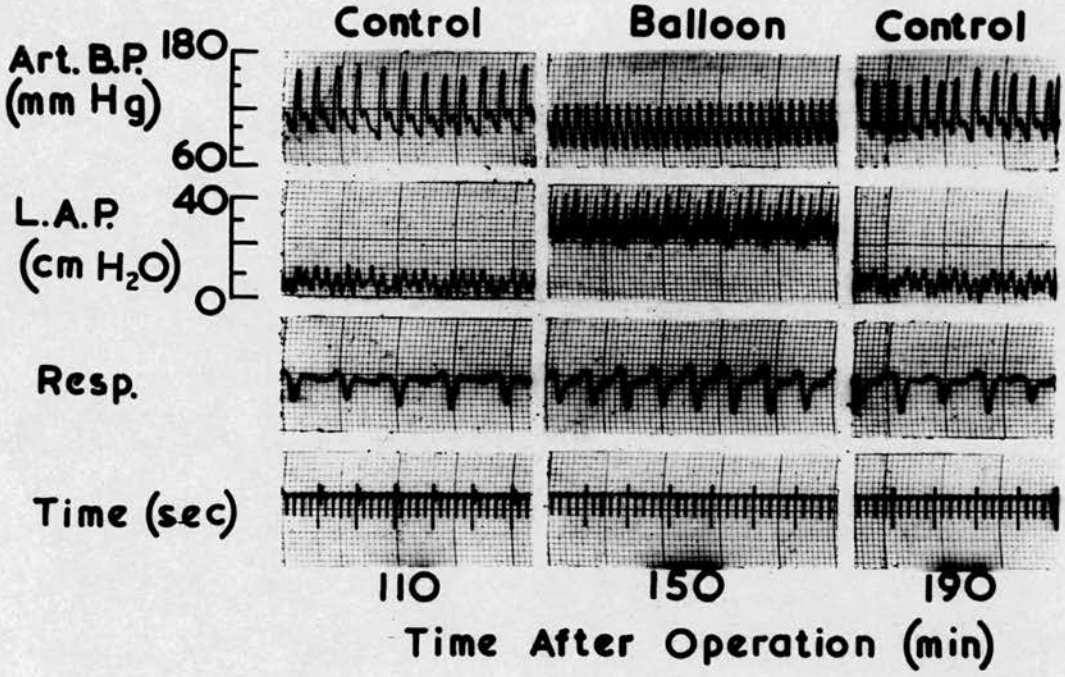

Fig. 2. Record of arterial pressure, left atrial pressure and respiration, before, during and after inflation of a balloon in the left atrium. Time marker in seconds and fifths of a second.

inflation was found to be significantly lower than during the control periods ($P = 0.01$).

In addition to changes in mean arterial pressure there was usually a decrease in pulse pressure during balloon inflation. Fig.2 shows the record of an experiment in which the most common cardiovascular changes were seen; there is an increase in heart rate, a marked fall in systolic pressure and a smaller fall in diastolic pressure so that pulse pressure is reduced. The contour of the pulse wave has also been changed by balloon inflation. Compared with the control periods there is a rapid rise of pressure during systolic ejection from the ventricle, a high dicrotic wave and a slow decline during diastole. Similar changes were seen in experiments in which there were only small changes in heart rate (Fig.3); in this experiment there was a reduction in both systolic and diastolic pressure during balloon inflation. Even when there was little change in either systolic, diastolic or mean arterial pressure the contour of the pulse wave was altered throughout the period of inflation. Thus in Fig.4 during balloon inflation there was a very rapid rise in pressure during ventricular systole followed at first by a rapid fall of pressure and then a more gradual decline. Similar changes to these may be seen in the early stages of haemorrhage (Wiggers, 1949, p.803). These changes in the pulse contour are characteristic of diminished distensibility of the vessels and may also indicate an augmentation of ventricular contraction and shortening of systole such as occurs when adrenaline is given (Wiggers, 1952). These effects could be produced by increased sympathetic activity

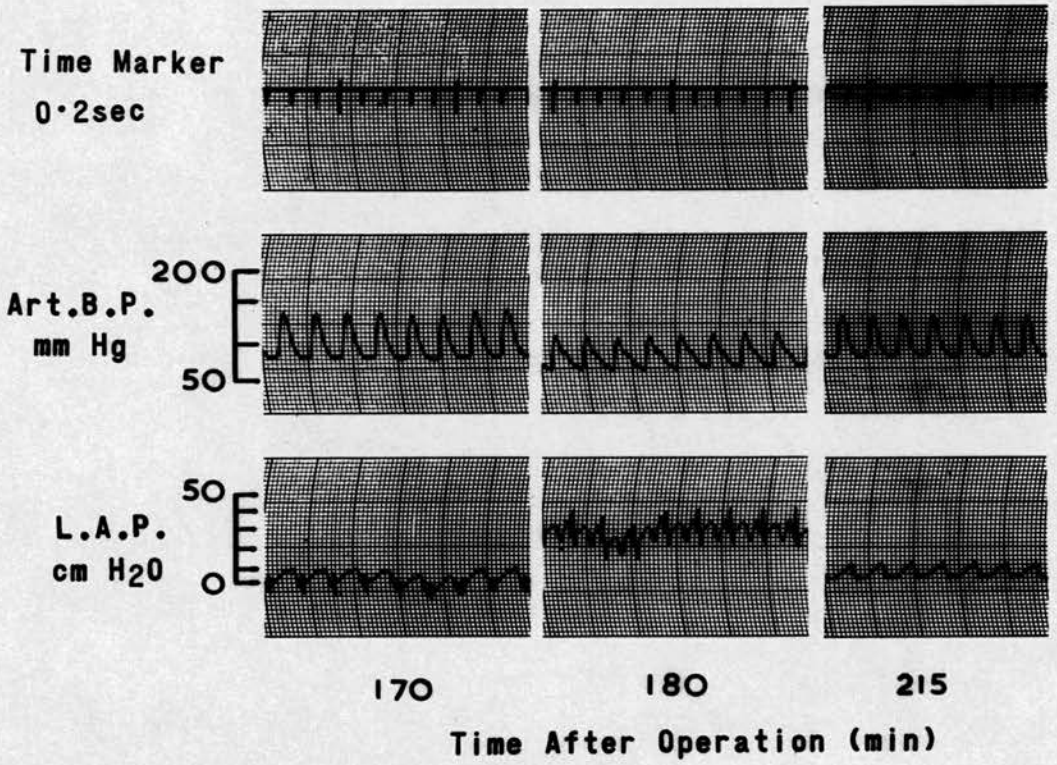

Fig. 3. The effect of inflating a balloon in the left atrium. Balloon inflated at 175 min and deflated at 205 min.

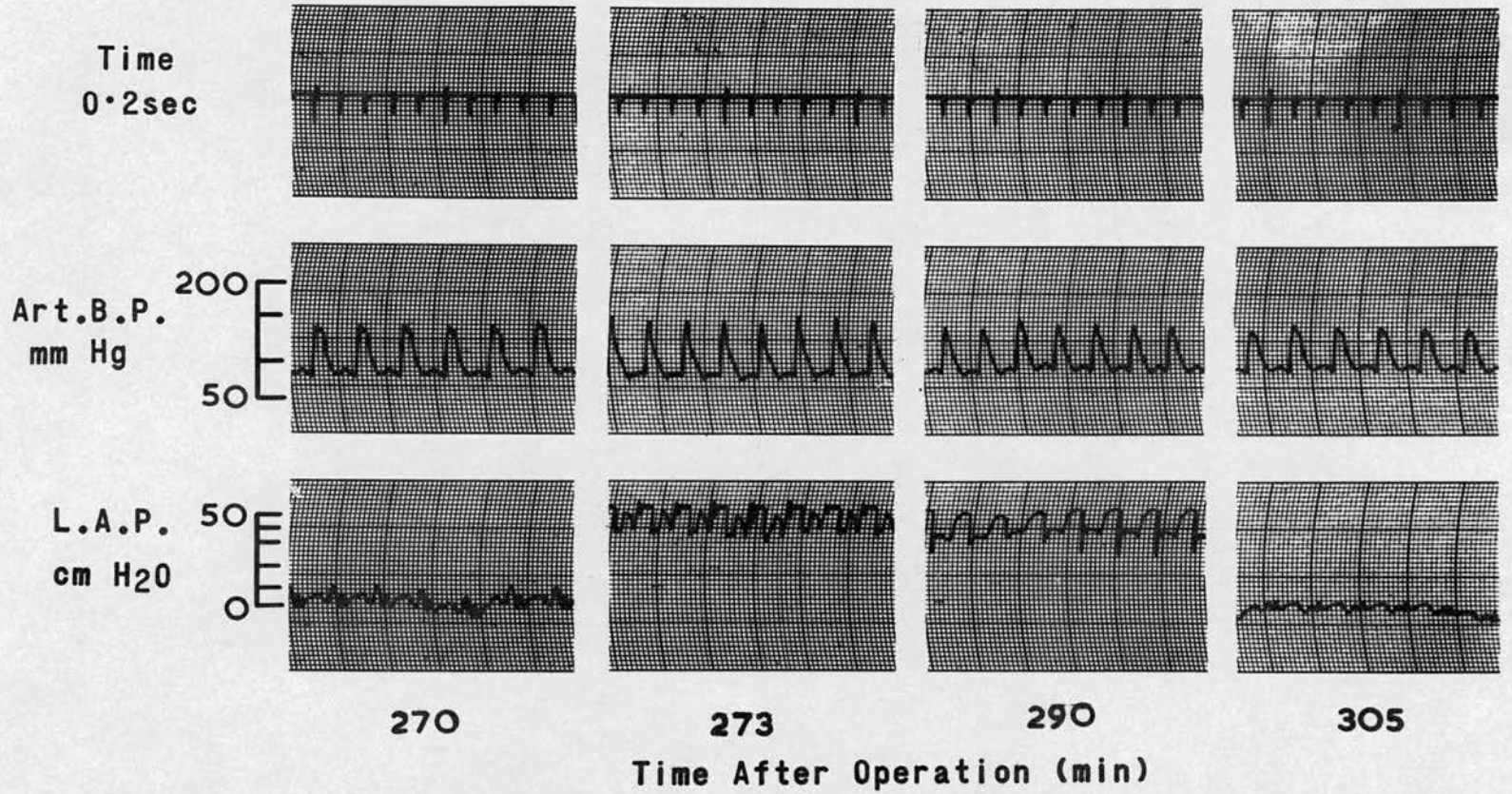

Fig. 4. The effect of inflating a balloon in the left atrium. Balloon inflated at 270 min and deflated at 300 min.

affecting peripheral vessels and the heart, either directly through nervous pathways or following an increased release of catecholamines from the adrenal medulla. There was no change in pressure in the inferior vena cava at the level of the renal veins in three experiments in which this was measured.

There was no relationship between the magnitude of the fall in arterial pressure and the rise in left atrial pressure over the range used in these experiments. However if the balloon was over-inflated atrial pressure rose further and systemic arterial pressure fell steeply; under these circumstances urine flow ceased.

The heart rate in these experiments was between 75 and 200 beats/min during the control periods and increased to about 200 beats/min when the balloon was inflated in the left atrium. When the balloon was deflated heart rate did not immediately return to its former level but gradually decreased over 5 - 10 minutes. The largest percentage increases in heart rate occurred in those experiments when the initial heart rate was low. There was no relationship between the fall in blood pressure and the change in heart rate, for example in experiment 8 (b) Table 2 there was little change in arterial pressure but a very marked increase in heart rate, whereas in experiment 7 (a) when arterial pressure fell 30 mm Hg there was relatively little increase in heart rate. Entirely similar heart rate changes were seen in animals artificially respired thus the increase in heart rate was not dependant upon increased respiratory movements.

In fourteen of these experiments the chest was closed and the

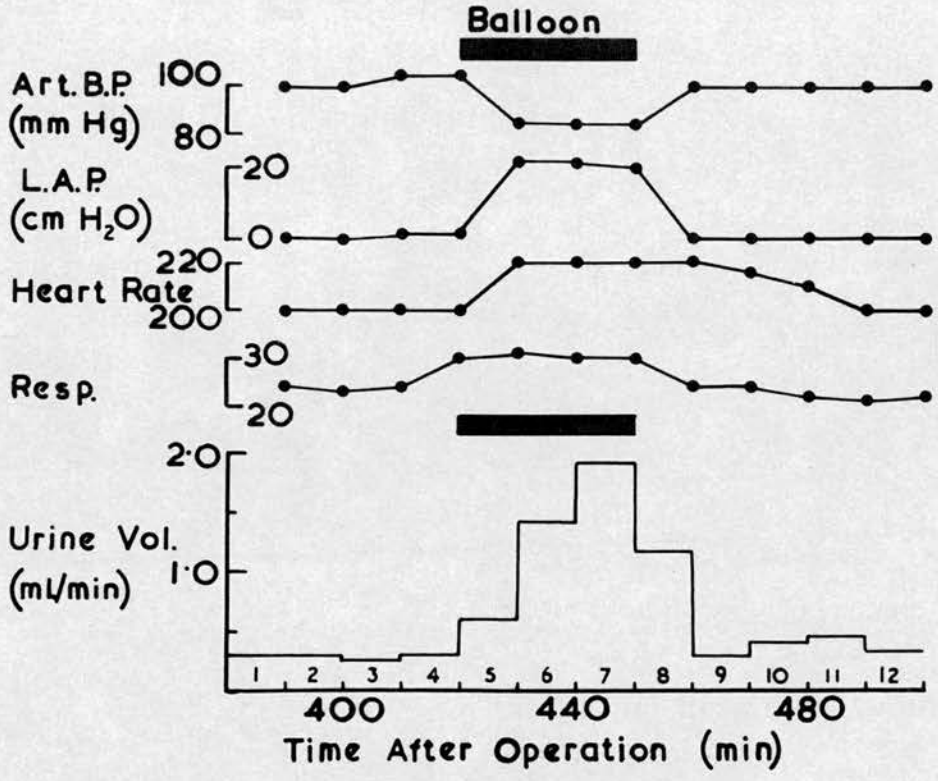

Fig.5. Effect of inflating a balloon in the left atrium for the 30 min indicated by the solid bar. From above downwards femoral arterial pressure, heart rate, respiratory rate and urine flow.

animals breathed spontaneously. Inflation of a balloon in the left atrium caused an immediate increase in both rate and depth of respiration (Fig.2). When this occurred the muscular movements associated with respiration became more vigorous and were often accompanied by movements of the limbs. No measurements were made of respiratory volumes but the changes in respiratory rate are listed in Table 2. After deflation respiratory rate did not always return to its former level but there was usually a progressive increase in respiratory rate throughout the experiment. Since manoeuvres which increase the rate and depth of respiration also cause diuresis (see page 108) the effect of maintaining constant artificial respiration was tested. In one animal the chest was reopened, in four the chest was not closed; intermittent positive pressure respiration was maintained at a constant rate and depth throughout the experiment. Inflation of the balloon in these experiments did not provoke any respiratory movements or an increase in other muscular movements. Changes in arterial pressure and heart rate were similar to those in animals breathing spontaneously.

Inflation of a balloon in the left atrium therefore caused a fall in arterial pressure, an increased heart rate and an increased respiratory rate, but these three parameters appeared to change quite independently of one another.

(b). THE EFFECT ON URINE FLOW.

Inflating a balloon in the left atrium usually led to an increase in urine flow (Table 2). Figure 5 shows the result of an experiment similar to those illustrated by Henry et al. (1956) in which a balloon was inflated in the left atrium and inflation

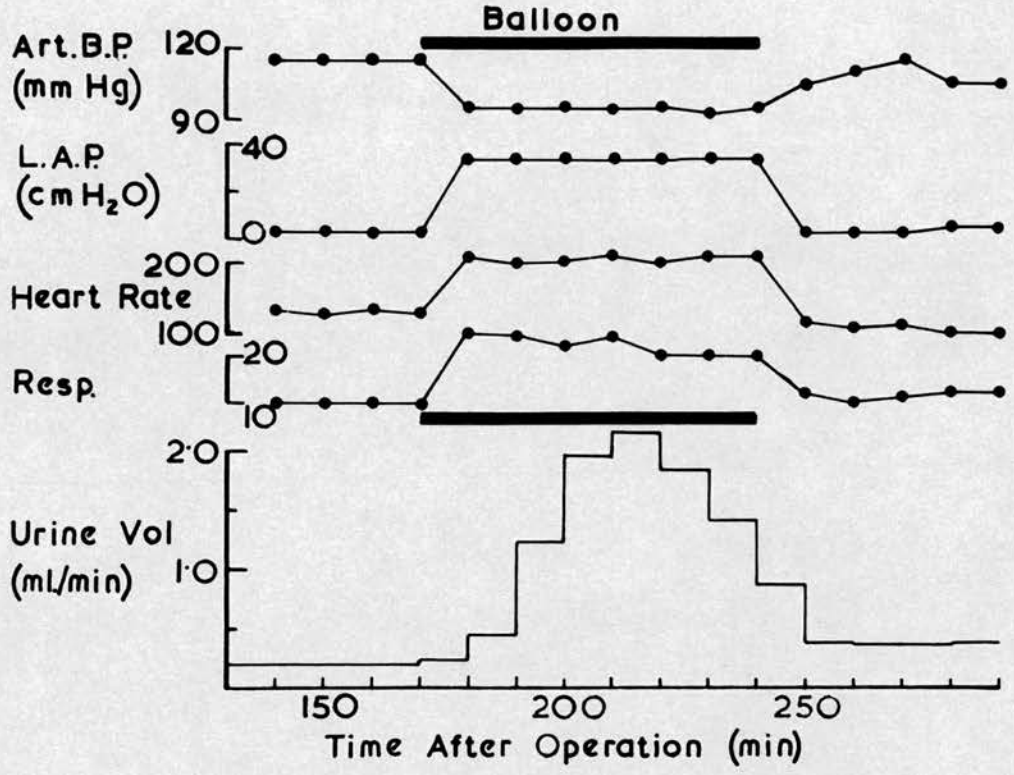

Fig. 6. Effect of inflating a balloon in the left atrium for 70 min. Conventions as in Fig.5.

maintained for 30 minutes. In response to the obstruction produced by the balloon urine flow from the two kidneys increased gradually from 0.3 ml./min to reach 1.9 ml./min after 30 min, and then decreased when the balloon was deflated. Sometimes during the first ten minutes of inflation urine flow decreased as in Fig.12; the earliest noticeable increase in urine flow began about 5 mins after inflation and more usually began after 10 - 15 minutes. The peak rate of urine flow was reached in the last period of inflation or in the first ten minutes of deflation. If inflation of the balloon in the left atrium was maintained for periods longer than 30 min the diuresis began to decrease despite the continued distension of the atrium. Fig.6 shows an experiment in which a balloon was inflated for 70 minutes. Urine flow increased to reach a maximum after 50 min and thereafter decreased although the high left atrial pressure, low arterial blood pressure and raised heart and respiratory rates were maintained. This was the most prolonged diuresis observed and on two other occasions when inflation was continued the diuresis began to fall off after 30 - 40 min; Henry et al. (1956) show a similar record.

To present the results of all experiments in which the balloon in the left atrium was inflated for 30 min the results are plotted in Fig.7 in a form similar to that used by Henry et al. (1956). The mean rate of urine flow (ml./min) for the 40 min preceding the test and the 40 min following the diuresis (i.e. the mean of urines 1, 2, 3, 4, 9, 10, 11, 12 in Fig.5) was regarded as the control rate, to be compared with the mean rate of urine flow during the diuresis (i.e. the mean of urines 6, 7, 8 in Fig.5). The continuous

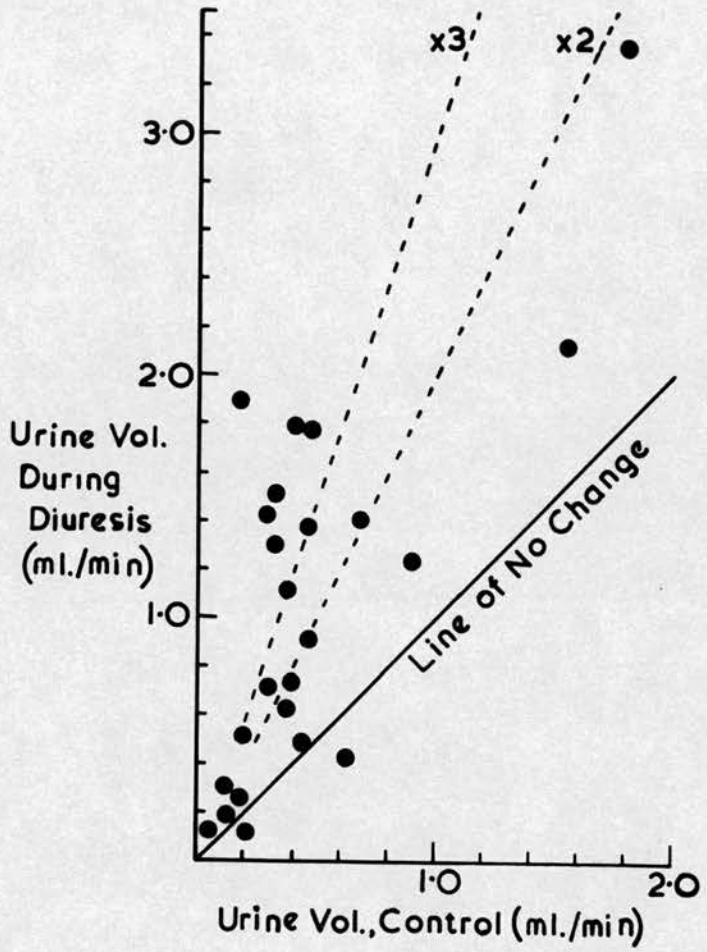

Fig.7. Results of twentyfour balloon inflations in eighteen dogs. Urine volume during the diuresis compared with urine volume during the control periods. The interrupted lines indicate diuresis of two and three times the control values.

line separates two observations in which urine flow decreased from twenty-two in which there was an increase. The interrupted lines separate nine observations when the urine flow during the diuresis was 1 - 2 times that during the control period, six observations 2 - 3 times and seven observations more than 3 times the control flow. The scatter of these observations is similar to that shown in the corresponding figure of Henry et al. (1956). The small size of the diuresis is illustrated by the fact that on only two occasions did the urine flow exceed 2 ml./min compared with 6 ml./min usually attained during water diuresis in the conscious dog (Fig.11). Whilst the results in Fig.7 leave no doubt that inflation of the balloon in the left atrium did produce a diuresis detailed examination of the response must be confined to examples where the diuresis was at least twice the control flow. A smaller response could not clearly be recognised against the variations within the control periods and descriptions of its time course and of the changes in urinary composition were impossible.

The size of the response varied not only from dog to dog but also in successive inflations in the same dog. It was not possible to predict from arterial pressure, left atrial pressure, heart rate or respiratory rate either before or during balloon inflation whether such an inflation would cause a moderate or only an insignificant diuresis. Usually urine flows from the two kidneys were equal but there were occasions when the flows differed although there were usually similar directional changes. Sometimes the difference

DOG NO.		V ml/min.	U_{Na} moles	$U_{Na}V$ m-mole min	U_K moles	U_KV m-mole min	U_{NH_4} moles	$U_{NH_4}V$ m-mole min	Uosm osmoles	UosmV m-osmole min	pH.
9(a)	B	0.24	0.32	0.073	0.14	0.032					
	D	0.71	0.14	0.09	0.07	0.05					
	A	0.39	0.24	0.093	0.15	0.06					
9(c)	B	0.40	0.22	0.086	0.12	0.045					
	D	1.37	0.07	0.093	0.03	0.04					
	A	0.54	0.20	0.11	0.11	0.06					
12 (a)	B	2.28	0.08	0.2	0.03	0.074					
	D	3.34	0.05	0.19	0.02	0.072					
	A	1.36	0.14	0.2	0.05	0.07					
13(a)	B	0.34					0.057	0.02	1.5	0.51	7.0
	D	0.62					0.06	0.038	0.7	0.44	6.2
	A	0.42					0.093	0.035	1.15	0.44	5.8
14(a)	B	0.12	0.20	0.023	0.11	0.015	0.06	0.007	0.92	0.11	7.0
(right)	D	0.71	0.04	0.026	0.03	0.022	0.016	0.013	0.21	0.17	7.0
	A	0.15	0.15	0.025	0.09	0.014	0.04	0.007	0.90	0.14	6.9
14(c)	B	0.17	0.3	0.05	0.08	0.015					6.8
(right)	D	0.96	0.02	0.016	0.03	0.024					6.9
	A	0.15	0.06	0.009	0.09	0.015					7.0
22(a)	B	0.20	0.10	0.02	0.17	0.036					7.0
	D	1.42	0.02	0.02	0.03	0.027					5.8
	A	0.39	0.11	0.04	0.08	0.031					
23(a)	B	0.15	0.31	0.041	0.13	0.016			2.3	0.3	7.0
	D	0.51	0.09	0.042	0.06	0.015			0.81	0.32	5.8
	A	0.24	0.22	0.052	0.07	0.017			1.41	0.33	5.7
26(a)	B	0.24	0.04	0.014					0.95	0.27	7.0
	D	1.3	0.01	0.013					0.28	0.33	7.0
	A	0.43	0.04	0.013					0.74	0.29	5.8
28(a)	B	0.19	0.02	0.004	0.07	0.013			0.76	0.16	6.8
	D	1.79	0.004	0.006	0.02	0.02			0.13	0.2	6.0
	A	0.63	0.015	0.007	0.04	0.02			0.29	0.17	6.8
MEANS	B	0.41	0.15	0.052	0.09	0.023			1.3	0.27	
	D	1.28	0.05	0.06	0.03	0.03			0.43	0.29	
	A	0.47	0.13	0.06	0.08	0.031			0.9	0.27	

Table 3. Results of analysis of the urine in ten of the experiments listed in Table 2. In one experiment the urine from only one kidney was analysed.

was due to blockage of the ureteric catheter and traction on the catheter would then produce a sudden spurt of urine; there were occasions when no cause for the unequal flow could be found.

To obtain a diuretic response Henry et al. (1956) thought it necessary to have the chest closed and the animal breathing spontaneously. Figure 18 shows one experiment during which intermittent positive pressure respiration was maintained constant whilst balloon inflation caused typical changes in arterial pressure, left atrial pressure and heart rate and a diuresis of four times the control flow. A diuresis was produced in an open-chested animal on four other occasions (Table 2).

Henry et al. (1956) stated that 2 - 4 hours should elapse after the operation before inflating the balloon as this gave time for a decrease in the level of circulating antidiuretic hormone. In the present series of experiments this practice was followed, and it was usually necessary to wait several hours before urine flow reached a steady control level and balloon inflation could be made. However, diuresis was observed on each of two occasions when a balloon was inflated within one hour of the operation; Fig.18 illustrates this finding the diuresis being produced 40-70 min after completion of the operation.

(c). THE EXCRETION OF SOLUTES.

Analysis of the urine to determine the concentration of sodium and potassium was made in the majority of the experiments. However only those instances in which there was an increase in urine flow of about 0.5 ml./min will be examined in detail. The results of

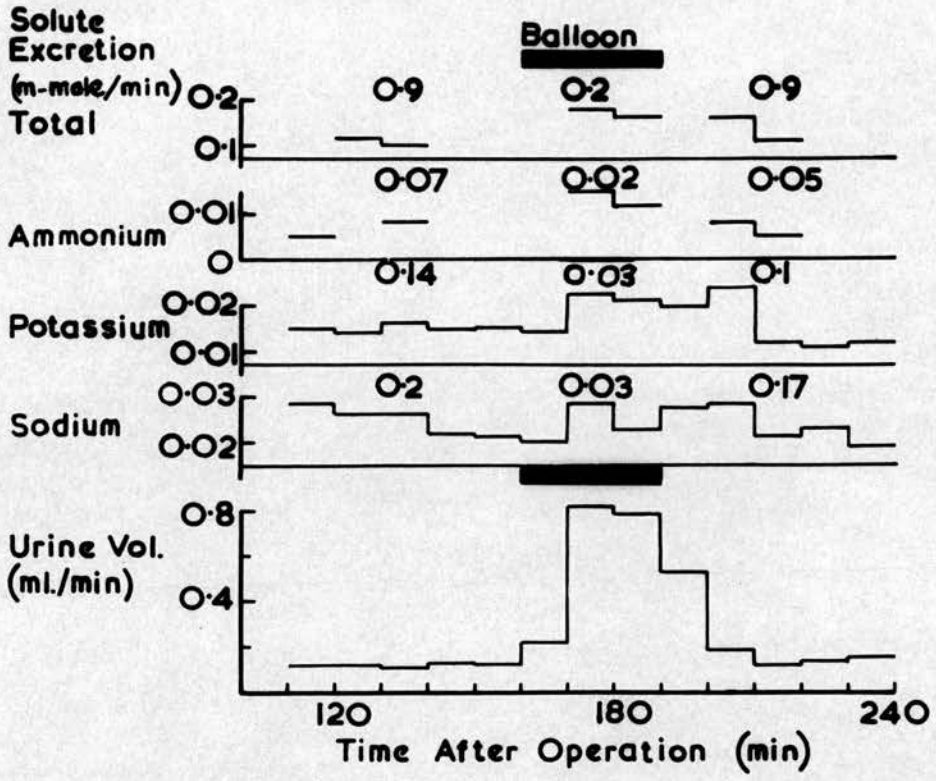

Fig.8. Composition of urine and rates of excretion from right kidney during inflation of a balloon in the left atrium. From above downwards urine solute excretion, total solute, ammonium, potassium and sodium and urine flow. Figures written above each line show urine concentration (M).

analysis of the urine in these experiments appear in Table 3. When the urine flow from the two kidneys was about equal then the urine samples were mixed and this pooled sample analysed; when the flows were unequal then the urine from only one kidney was analysed and in these cases the figures for concentration and excretion of solutes and urine flow, in Table 3, refer only to this one kidney.

In Fig.8 the results are shown of analysis of the urine from the right kidney in one experiment. In response to inflation of a balloon in the left atrium urine flow increased from 0.12 ml./min to 0.8 ml./min an increase of about six times, whilst during the same period the excretion of the solid constituents in the urine increased by less than 70%; thus the concentrations of the various solutes fell to about one-fifth of the control values. This was the most usual change found and the concentration of the solutes always decreased when there was an increase in urine flow. Increases in sodium excretion were not seen particularly when the urine flow response was small, as was suggested by Henry (1955) and there was no evidence for the existence of two mechanisms, one affecting urine flow and the other causing changes in sodium excretion.

The total solute concentration in the urine was estimated in five experiments. Whilst urine flow increased to an average of 3.5 times the control flow (Table 3) the solute concentration fell by almost this amount so that the excretion of solutes remained relatively unchanged. Solute concentration in the plasma was not measured but it is likely that on at least one occasion (Table 3, 28 (a)), when urine solute concentration fell to 0.13 osmoles, the

urine was hypotonic with respect to plasma.

The pH of the urine during the control periods was usually about 7.0 and showed inconsistent changes during balloon inflation. On several occasions the urine became more acid during balloon inflation (Table 3) but this was not an essential feature of the diuresis, as frequently pH was unchanged.

The changes in ammonium excretion were similar to those of other solutes in the two experiments in which this was measured.

The urine was found to contain a reducing substance when tested with Benedicts qualitative reagent, but tests with Benedicts quantitative reagent did not give the colour changes typical of those produced by glucose. However an estimate of the concentration of reducing substances was made using Fine's modification of Benedict's qualitative test (Fine, 1935), and the concentration of reducing substance was found to decrease as the urine flow increased so that the excretion of reducing substances remained constant.

Plasma glucose concentration was estimated in one dog as 100mg/100 ml. and in another dog 80mg/100 ml. and both showed only a small increase of about 10 mg/100 ml. when a balloon was inflated in the left atrium. Total plasma solids measured 7.33g/100g H_2O in one dog and 7.65g/100g H_2O in another; there were no significant changes when the balloon was inflated in the left atrium.

2. URINE FLOW IN ANIMALS UNDER CHLORALOSE ANAESTHESIA.

The significance of the urinary response to inflation of a balloon in the left atrium can only be assessed when an examination has been made of other variations in urine flow which occur in animals which have been anaesthetized with chloralose and subjected to a

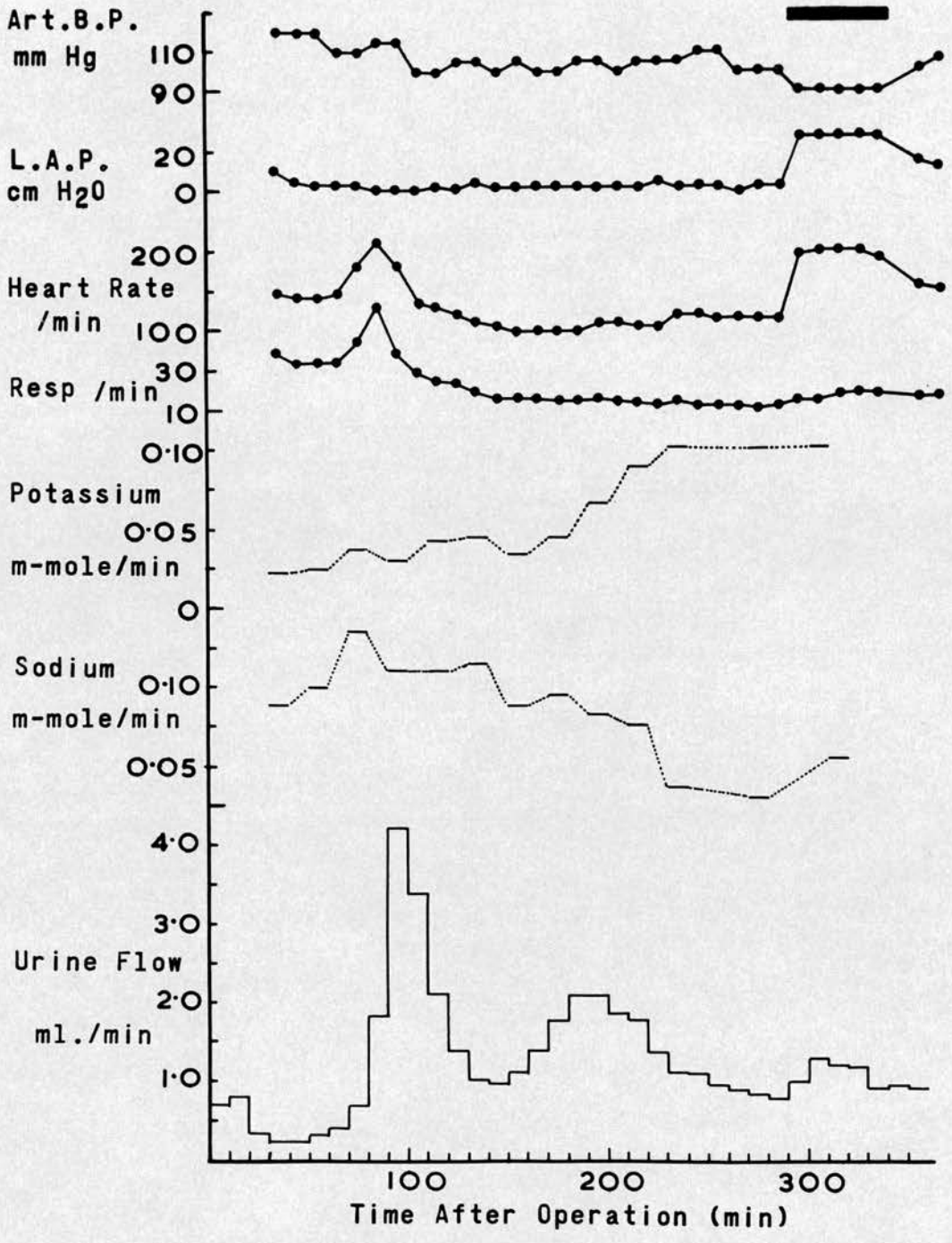

Fig.9. Spontaneous variations in urine flow in a chloralose anaesthetized dog. A balloon was inflated in the left atrium during the period indicated by the solid bar.

traumatic surgical operation. Whilst animals were not specifically prepared for this purpose the necessity to wait for a steady urine flow lasting about 40 minutes to give a control level before balloon inflation meant that there was ample opportunity during the experiments already described to observe changes in urine flow other than those caused by balloon inflation.

Although the ureters were catheterized at the beginning of the operation it was not practicable to collect and measure the urine until all the surgical procedures were completed. However, during the operation the urine did run into test-tubes and there was usually less than 10 ml. of urine collected from each kidney by the time the operation was finished; that is about 90 min collection. In about half of the experiments urine flow was low immediately after the operation (less than 0.1 ml./min) and increased slowly over the next 2 - 4 hours to reach a flow of between 0.1 - 0.4 ml./min; this was the control flow at which most of the tests were carried out. In these animals after balloon inflation urine flow returned to about this level and remained there until the next balloon inflation 1 - 2 hours later (Fig.12). In the other experiments urine flow was more rapid from the start and either increased gradually to reach 0.2 - 0.4 ml./min or showed more marked fluctuations. In three experiments there were large changes in urine flow; one of these experiments is illustrated in Fig.9. The large and rapid changes in urine flow dwarf the smaller response to balloon inflation. During such spontaneous changes in urine flow the concentration of sodium and potassium in the urine decreased so that the excretion of these substances was little changed, thus resembling the response to

balloon inflation. The spontaneous increases in urine flow sometimes seemed to occur when depth of anaesthesia had become lighter and it will be seen in Fig.9 that a transient increase in heart and respiratory rates immediately preceded the first diuresis. During this period the animal had shown pronounced muscular twitching. However, it was never possible to reproduce such changes in urine flow by purposely allowing the anaesthetic to become lighter. These spontaneous increases in urine flow affected both kidneys and in one animal with one kidney denervated there was a large spontaneous diuresis which affected both kidneys to the same degree.

Infusions of dog blood, plasma, dextran (Dextran 6%, Benger Laboratories Ltd.), or sodium chloride solution 0.9g/100 ml. were sometimes given during the experiments. Henry et al. (1956) suggested that infusions of dog blood or bovine albumin would enhance the diuretic response to balloon inflation. Whilst infusion of these substances caused transient increases in urine flow in 9 out of 14 infusions it was not possible to confirm that the response to balloon inflation was any greater after inflation than it otherwise would have been. During the diuresis following infusion of blood, plasma or dextran, sodium concentration fell so that sodium excretion showed only a small increase (Fig.15). When saline was infused the increase in urine flow was accompanied by an increased excretion of sodium.

Some evidence has already been presented suggesting that during inflation of a balloon in the left atrium there is an increased activity of the sympathetic nervous system or a release of noradrenaline.

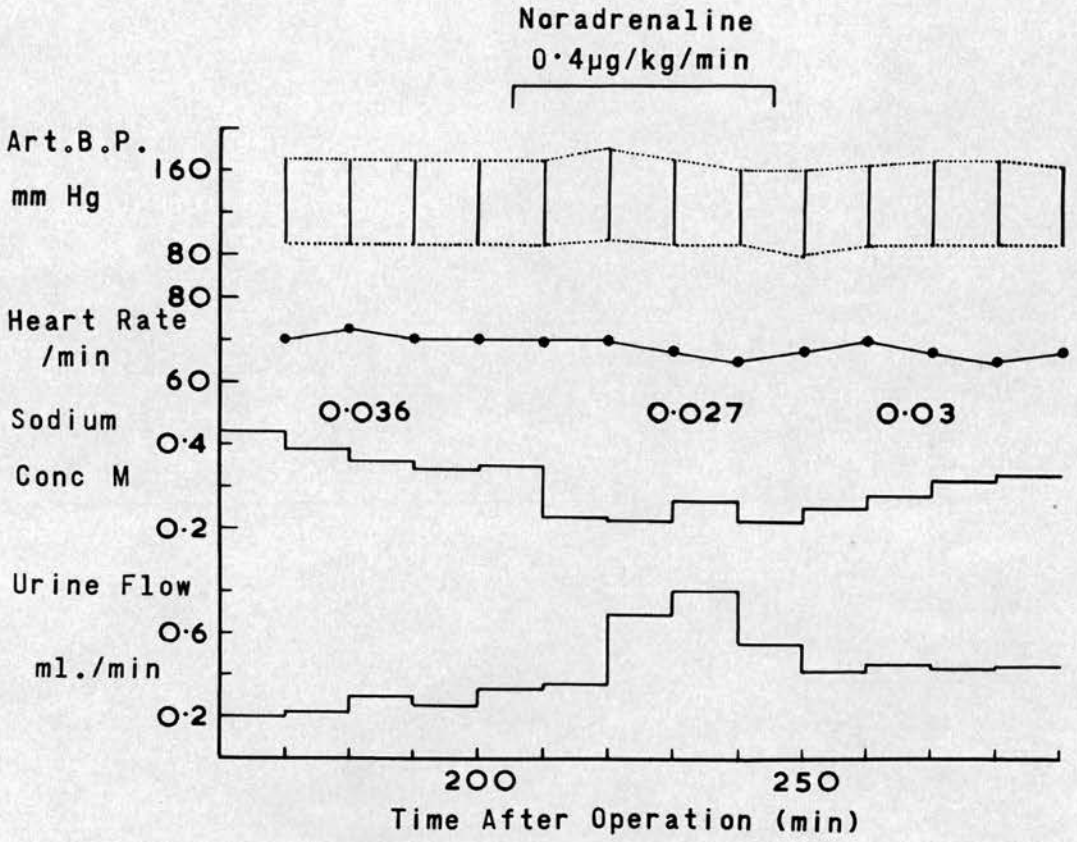

Fig.10. Effect of infusion of noradrenaline 0.4 μg/kg/min. From above downwards, systolic and diastolic arterial pressure, heart rate, sodium concentration and urine flow. The figures are the excretion of sodium (m-mole/min).

Infusions of noradrenaline were therefore given to three dogs anaesthetized and prepared as for the experiments on atrial balloon inflation. Eleven infusions were given in three dogs at a rate of 0.1 - 0.8 μg/kg/min and infusion was usually continued for half an hour. Four of these infusions were accompanied by an increase in urine flow and in the other seven infusions there was no change in urine flow. One experiment is shown in Fig.10; infusion of noradrenaline at a rate of 0.4 μg/kg/min caused small changes in blood pressure and heart rate but urine flow doubled. During the increased rate of urine flow the concentration of sodium in the urine decreased and sodium excretion therefore remained constant. On each of the other three occasions when urine flow increased during infusion of noradrenaline sodium excretion remained constant.

Thus in these animals anaesthetized with chloralose and surgically traumatized increasesin urine flow may occur either spontaneously or following infusion of fluids such as blood, plasma or dextran or during infusions of noradrenaline, as well as during inflation of a balloon in the left atrium. Whichever manoeuvre was associated with the increase in urine flow, the concentration of sodium and potassium fell so that the excretion of these substances remained relatively constant. The only exception to this was following infusion of 0.9% sodium chloride solution when sodium concentration remained constant and sodium excretion was increased.

3. THE EFFECT OF OBSTRUCTING THE MITRAL ORIFICE DURING AN INFUSION OF VASOPRESSIN.

(a) ASSAY OF THE ANTIDIURETIC ACTIVITY OF A COMMERCIAL EXTRACT OF VASOPRESSIN.

If the diuretic response to atrial distension is the result of inhibition of the release of antidiuretic hormone it should be possible to prevent the diuresis by infusion of vasopressin at an appropriate rate. The antidiuretic hormone from the pituitary of the pig is lysine vasopressin (Popenoe, Lawler & du Vigneaud, 1952) whereas in most other species including the ox and the dog the active principle is arginine vasopressin. Solutions of arginine vasopressin and lysine vasopressin assayed to contain the same pressor activity have equal antidiuretic activity when injected intravenously in rats but in conscious dogs lysine vasopressin has only one-sixth of the antidiuretic activity of arginine vasopressin (van Dyke, Engel & Adamsons, 1956). Commercial preparations of vasopressin are assayed only for their pressor activity and at least in recent years have contained a proportion of lysine vasopressin. The two batches of Pitressin (Parke, Davis & Co.) used in these experiments contained both arginine vasopressin and lysine vasopressin with the lysine vasopressin probably predominating (personal communication, Parke, Davis & Co.). It is possible that doses quoted by earlier authors as adequate to inhibit water diuresis may apply to preparations containing only arginine vasopressin. The antidiuretic activity of the batches of Pitressin used in these experiments was therefore tested on a conscious dog undergoing water diuresis.

For these experiments an alsatian bitch 'Kim' was used; she had a perineotomy and had been trained to lie quietly on a table. The experiments were carried out at the same time on consecutive days for two weeks. At 10.00 hours each day a stomach tube was passed and 100 ml. 0.9% sodium chloride solution and 200 ml. tap

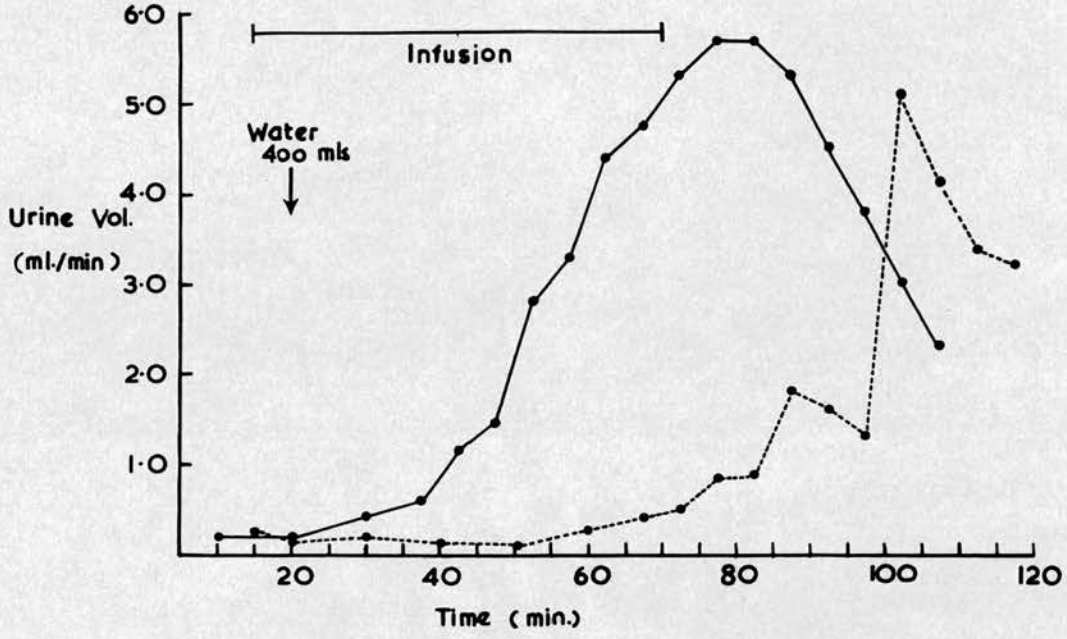

Fig.11. Water diuresis in a conscious dog. Zero time was 1400 hours on each day. Infusion given of either 0.9% Na Cl solution 0.14 ml./min (continuous line) or 0.9% Na Cl solution containing vasopressin to give 0.009 m-u/kg/min. Tap water 400 ml. by stomach tube at time indicated.

water placed in the stomach, after which the animal was returned to her cage. At 14.00 hours a self-retaining catheter was inserted into the bladder and the animal laid on her side on a padded table. A fine bore nylon tube was inserted into a saphenous vein and connected to a motor driven syringe which delivered 0.14 ml./min 0.9% sodium chloride solution. On alternate days 'Pitressin' of either batch LY258J or LZ1094C was added to the sodium chloride solution to give the stated rate of infusion. Ten minutes later a stomach tube was passed and 400 ml. tap water placed in the stomach. Urine was collected into a graduated cylinder and its volume measured every five or ten minutes. The infusion was maintained for one hour and the urine was collected for a further hour. Occasionally after about an hour the animal became restless and struggled, and the experiment was then abandoned whether or not the struggling was associated with an inhibition of urine flow.

Whenever the experiment was made without vasopressin in the infusion a typical water diuresis was seen with maximal urine flow of 5 - 6 ml./min. Infusion of vasopressin of either batch at 0.009 m-u/kg/min always completely prevented the water diuresis appearing; when the infusion was stopped urine flow rose gradually to reach a rather lower peak value. Fig.11 shows the course of an experiment in which 0.9% sodium chloride solution was infused and another experiment in which vasopressin was added to the infusion. The complete suppression of the water diuresis until after the vasopressin infusion was stopped is clearly shown. Infusion of vasopressin at a rate of 0.0045 m-u/kg/min. did allow some increase

in urine flow following the administration of water. From these experiments it was concluded that infusion of 'Pitressin', of either of the batches used, at a rate of 0.009 m-u/kg/min was adequate to completely inhibit water diuresis in the conscious dog.

These experiments were designed so that the infusion had been running for 40 - 50 min at the time the peak of the water diuresis was expected. At this time endogenous release of antidiuretic hormone is minimal and inhibition of the water diuresis can be attributed entirely to the exogenous hormone. In the experiments in which a balloon was inflated in the left atrium vasopressin infusion was begun 40 - 50 min before the balloon was inflated and should therefore have reached a similar concentration in the experimental animal and be capable of inhibiting water diuresis in the complete absence of endogenous release of the hormone.

Verney (1947) suggests that infusion at about half the dose rate found here is adequate to inhibit water diuresis. Since the proportions of arginine vasopressin and lysine vasopressin were not known, no comparison can be made between these results and those of van Dyke, Engel & Adamsons (1956). However they gave vasopressin by a single intravenous injection and it is possible, that if the difference between the two vasopressins is a difference in the rate of inactivation, their activities may be more nearly similar when given by intravenous infusion.

(b). THE ACTIVITY OF VASOPRESSIN IN ANAESTHETIZED DOGS.

An attempt was made to produce a water diuresis in two dogs anaesthetized with chloralose. These dogs suffered surgical trauma

during cannulation of the femoral vessels and the trachea, and catheterization of the ureters; the chest was not opened. In one dog 400 ml. water was placed in the stomach via a stomach tube and this was followed by a gradual increase in urine flow from,0.3ml./min to 3 ml./min after an hour. At the same time, however, sodium excretion increased three times. An infusion of vasopressin 0.025m-u/kg/min was without any obvious effect on urine flow as although urine flow did fall to 2 ml./min after half an hour's infusion, it continued to fall when the infusion was stopped. A second dog was anaesthetized similarly and then given a priming dose of 120 ml. saline. An hour later an infusion of distilled water was given at a rate of 5 ml./min through a catheter whose tip lay in the right atrium. Urine flow increased slowly from 1 ml./min to reach 2 ml./min after an hour. Injection of vasopressin 2 m-u. followed by an infusion at a rate of 0.025m-u./kg/min produced an apparent mild inhibition of this diuresis but urine flow was reduced only gradually to reach 1.5 ml./min after 20 min. Injection of 5 m-u. vasopressin produced a similar small sluggish reduction in urine flow.

The time course and size of the diuresis in response to the administration of water by these routes is unlike that seen when similar volumes are given to conscious dogs. Doses of vasopressin more than adequate to completely inhibit water diuresis in conscious dogs had little demonstrable effect on the urine flow in the anaesthetized dogs. Thus the diuresis associated with the administration of water in these anaesthetized dogs cannot be

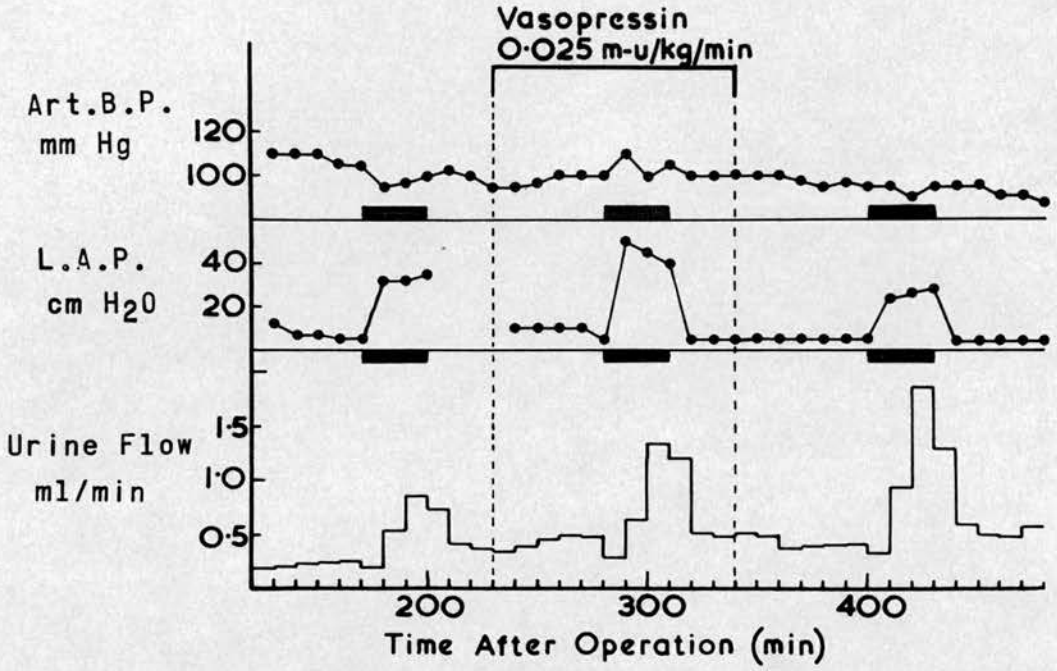

Fig.12. Diuresis produced by balloon inflation during infusion of vasopressin. Vasopressin infusion 0.025 m-u./kg/min was started 50 min before and continued until 30 min after the second inflation. From above downwards, femoral arterial pressure, left atrial pressure and urine flow.

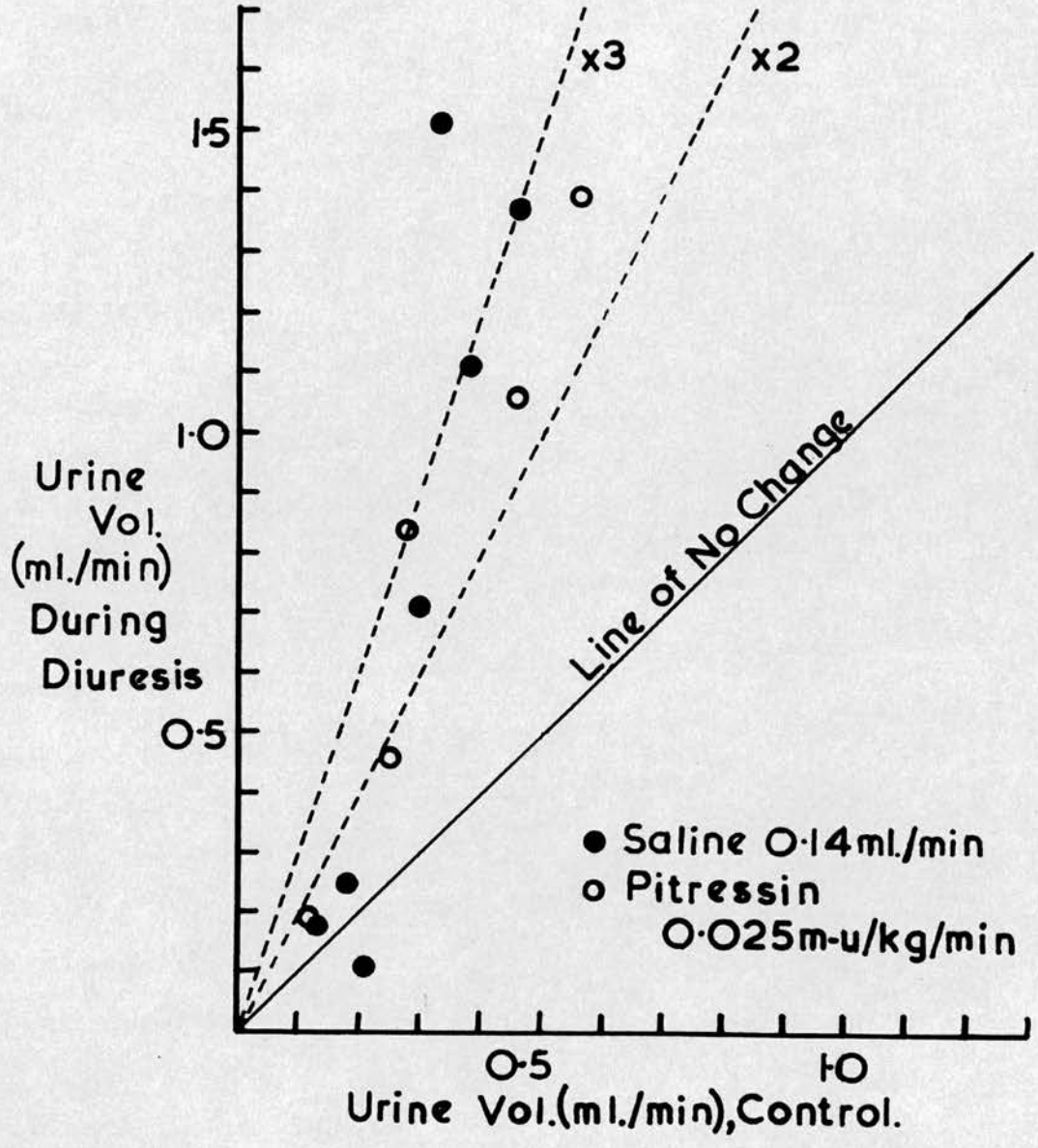

Fig.13. Twelve balloon inflations in five dogs. Urine flow during the diuresis compared with urine flow during control periods. During five inflations an infusion of vasopressin 0.025 m-u/kg/min was given (open circles).

considered to be a true 'water diuresis' that is due to a decrease in the release of antidiuretic hormone from the neurohypophysis.

(c). EFFECT OF INFUSION OF VASOPRESSIN ON THE DIURETIC RESPONSE TO MITRAL OBSTRUCTION.

As it was not possible to produce a satisfactory 'water diuresis' in traumatized, anaesthetized animals, it was not possible to assess what dose of vasopressin would be effective in preventing such a diuresis. A dose of vasopressin was therefore used more than adequate to prevent the appearance of water diuresis in the conscious dog but not so large that pressor effects might be anticipated.

Figure 12 shows the effect of inflation of a balloon in the left atrium by exactly the usual procedure but during an infusion of vasopressin. Saline 0.14 ml./min was infused throughout this experiment and vasopressin was added to the infusion during the period shown. Infusion at a rate of 0.025 m-u./kg/min started 50 min before the test and continued until 30 min afterwards had no effect on urine flow and in no way modified the diuretic response which wassimilar to the diureses in Fig.12 when no vasopressin was infused. Figure 13 shows the diuretic response on each of five occasions when a balloon was inflated in the left atrium during infusion of vasopressin 0.025 m-u./kg/min, and on seven occasions in the same five dogs when there was no infusion of vasopressin. Figure 14 depicts the effects produced by two balloon inflations made during infusion of vasopressin at a rate of 0.1 m-u./kg/min; on each occasion there was a diuresis of about twice the control

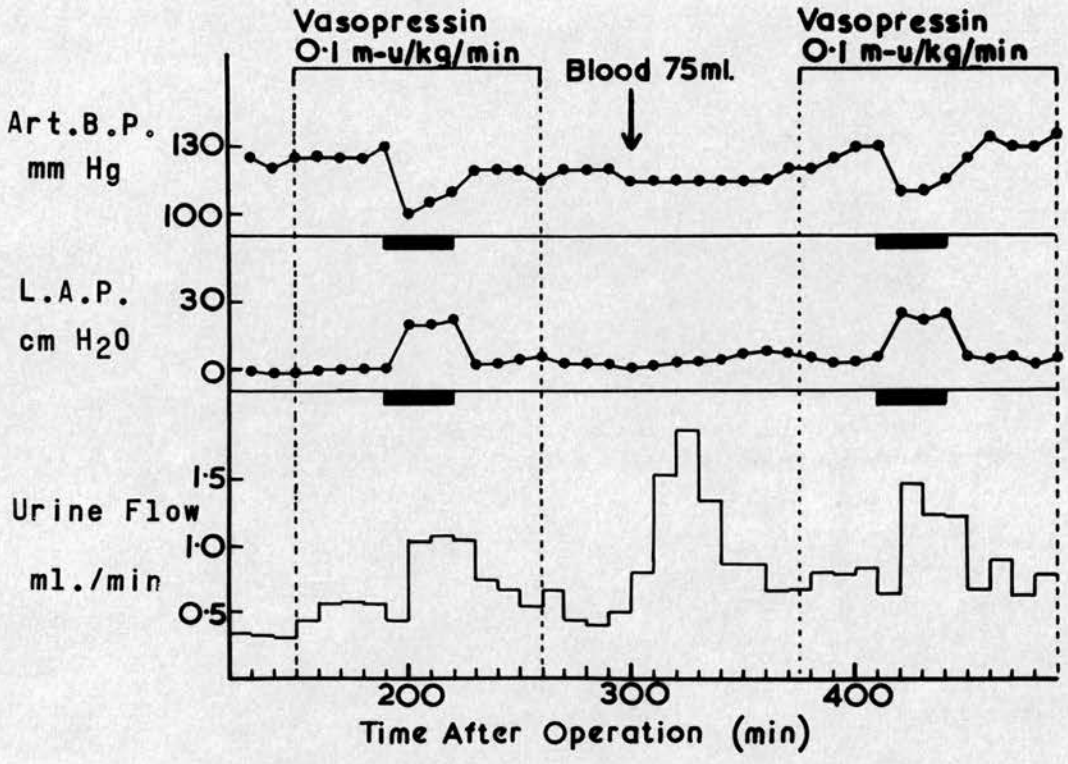

Fig.14. Two balloon inflations during infusion of vasopressin 0.1 m-u./kg/min. Conventions as in Fig.12. A diuresis following infusion of 75 ml. dog blood is also shown.

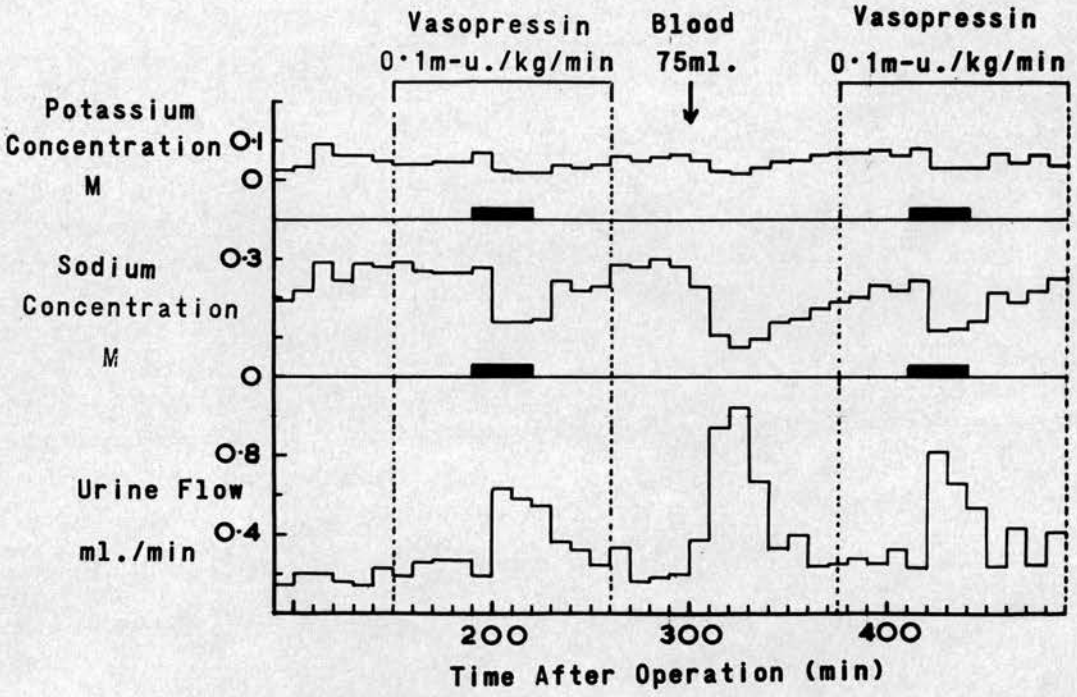

Fig.15. Two balloon inflations during infusion of vasopressin 0.1 m-u./kg/min. From above downwards, potassium concentration, sodium concentration and urine flow from left kidney. A diuresis following infusion of 75 ml. dog blood is also shown.

DOG NO.		V	U_{Na}	$U_{Na}V$	U_K	U_KV	Vasopressin
		ml/min	moles	m-mole/ Min	moles	m-mole/ min.	m-u/kg/min.
8a)	B	0.29					
	D	0.45					0.025
	A	0.26					
9(b)	B	0.46	0.2	0.09	0.15	0.07	
	D	1.06	0.1	0.096	0.07	0.05	0.025
	A	0.50	0.23	0.12	0.10	0.05	
10(a)	B	0.5	0.19	0.127	0.1	0.061	
(left)	D	0.93	0.03	0.042	0.05	0.064	0.025
	A	0.26	0.17	0.045	0.11	0.048	
11(b)	B	0.12					
	D	0.19					0.025
	A	0.18					
14(b)	B	0.13	0.05	0.006	0.125	0.017	
(right)	D	0.55	0.02	0.015	0.05	0.025	0.025
	A	0.15	0.07	0.01	0.16	0.023	
17(a)	B	0.25	0.27	0.07	0.05	0.012	
(left)	D	0.58	0.14	0.08	0.02	0.012	0.1
	A	0.31	0.24	0.076	0.04	0.013	
17(b)	B	0.28	0.21	0.06	0.07	0.02	
(left)	D	0.67	0.13	0.08	0.03	0.02	0.1
	A	0.31	0.24	0.076	0.04	0.013	
19(a)	B	2.0	0.13	0.27	0.055	0.11	
	D	2.3	0.11	0.26	0.04	0.10	0.1
	A	1.8	0.16	0.30	0.05	0.08	

Table 4. Results of eight inflations made during infusions of vasopressin. In three experiments the urine from only one kidney was analysed.

flow. Infusion at this rate caused no decrease in urine flow and in fact sometimes appeared to produce a small increase in urine flow; left atrial pressure and mean arterial pressure were unchanged. In one dog with a high rate of urine flow (2 ml./min) infusion of vasopressin 0.1 m-u./kg/min had no effect on urine flow and did not prevent the appearance of a further increase in urine flow (to 2.3 ml./min) when a balloon was inflated in the left atrium (Table 4).

The changes in urinary sodium and potassium concentration that occurred during balloon inflation in the presence of vasopressin were similar to those seen when no vasopressin was given (Fig.15, Table 4).

4. THE EFFECT OF DENERVATION OF A KIDNEY.

In five dogs the right kidney was denervated and 3 - 5 hours later when urine flow from both kidneys was steady a balloon was inflated in the left atrium (Table 5). In two dogs the flow from the denervated kidney was greater than from the innervated kidney but whatever the difference in flow between the kidneys the increase in urine flow was proportionately the same in the two kidneys. Figure 16 shows the result of one experiment; during the control period urine flow from the denervated kidney was about 50% greater than from the innervated kidney and when the balloon was inflated urine flow doubled in both kidneys. When the urine flow increased there was a decrease in the concentration of sodium and potassium in the urine from both kidneys so that the excretion of these

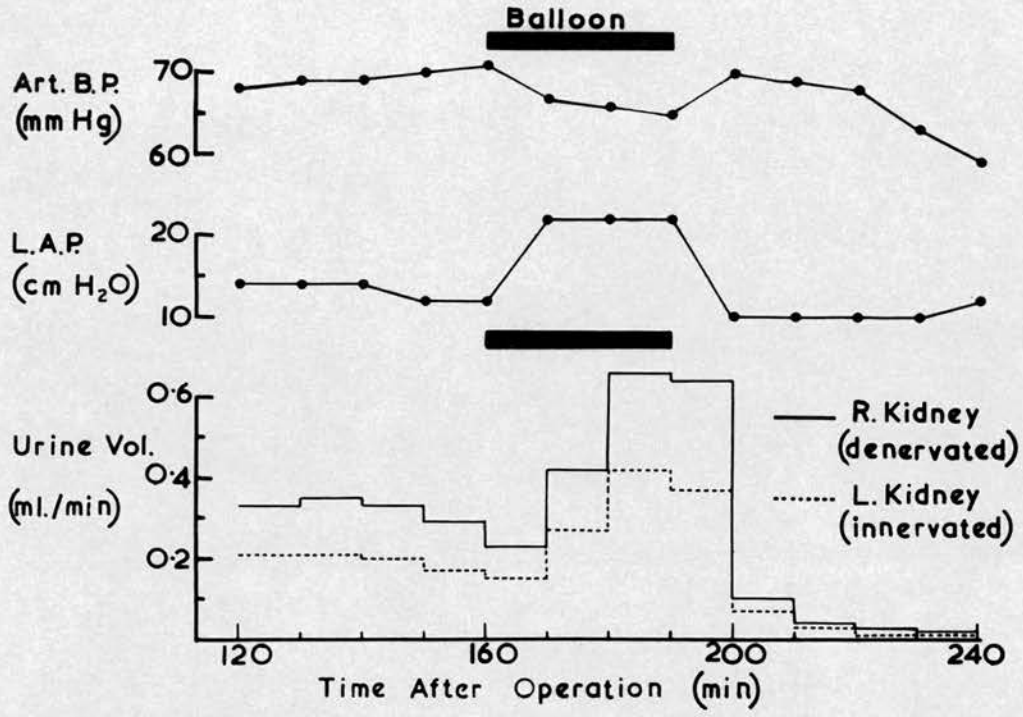

Fig.16. Effect of balloon inflation on a denervated kidney. From above downwards, femoral arterial pressure, left atrial pressure and urine flow. Continuous line, urine flow from denervated kidney; interrupted line, urine flow from innervated kidney. Chest open and positive-pressure artificial ventilation maintained unchanged throughout.

DOG NO.		INNERVATED KIDNEY V ml./min	DENERVATED KIDNEY V ml./min.
29	B	0.20	0.25
	D	0.35	0.57
	A	0.04	0.05
31	B	0.4	0.76
	D	0.48	0.72
	A	0.14	0.38
35	B	0.1	0.1
	D	0.11	0.19
	A	0.15	0.14
37	B	0.41	0.31
	D	1.14	0.82
	A	0.26	0.16
38	B	0.35	0.14
	D	0.49	0.36
	A	0.38	0.27
	B	0.29	0.31
Mean	D	0.51	0.53
	A	0.19	0.20

Table 5. Comparison of urine flow from innervated kidney and denervated kidney in five dogs before, during and after inflation of a balloon in the left atrium.

substances showed only small changes.

5. THE EFFECTS OF AN INTRAPERICARDIAL INJECTION OF A LOCAL ANAESTHETIC.

In three experiments a polyethylene tube was led into the pericardial cavity and placed so that its tip lay between the pulmonary veins in the oblique sinus of the pericardium. The incision in the pericardium was closed around this tube and the tubes from the left atrium and these were then led out of the chest. In these experiments after first obtaining a diuresis by inflating a balloon in the left atrium, 2 ml. of a 2% solution of amethocaine hydrochloride (Decicain 2%, Bayer Prod.) was injected into the pericardial cavity. There was little change in heart rate or blood pressure but after about five minutes both phrenic nerves became paralysed and the respiratory rate increased. Forty minutes after the injection of amethocaine a balloon was inflated in the left atrium; there was no change in urine flow in two of the experiments and inthe third urine flow decreased. About two hours after the amethocaine had been injected the diaphragm began moving normally and after a further half hour had apparently completely recovered. Inflation of the balloon in the left atrium then led to an increase in urine flow (Fig.17). Inflation of the left atrial balloon caused similar changes in left atrial pressure in the inflations before and after injection of amethocaine. In the experiment illustrated blood pressure fell markedly when the balloon was inflated after injection of amethocaine but in the other two experiments the blood pressure changes were

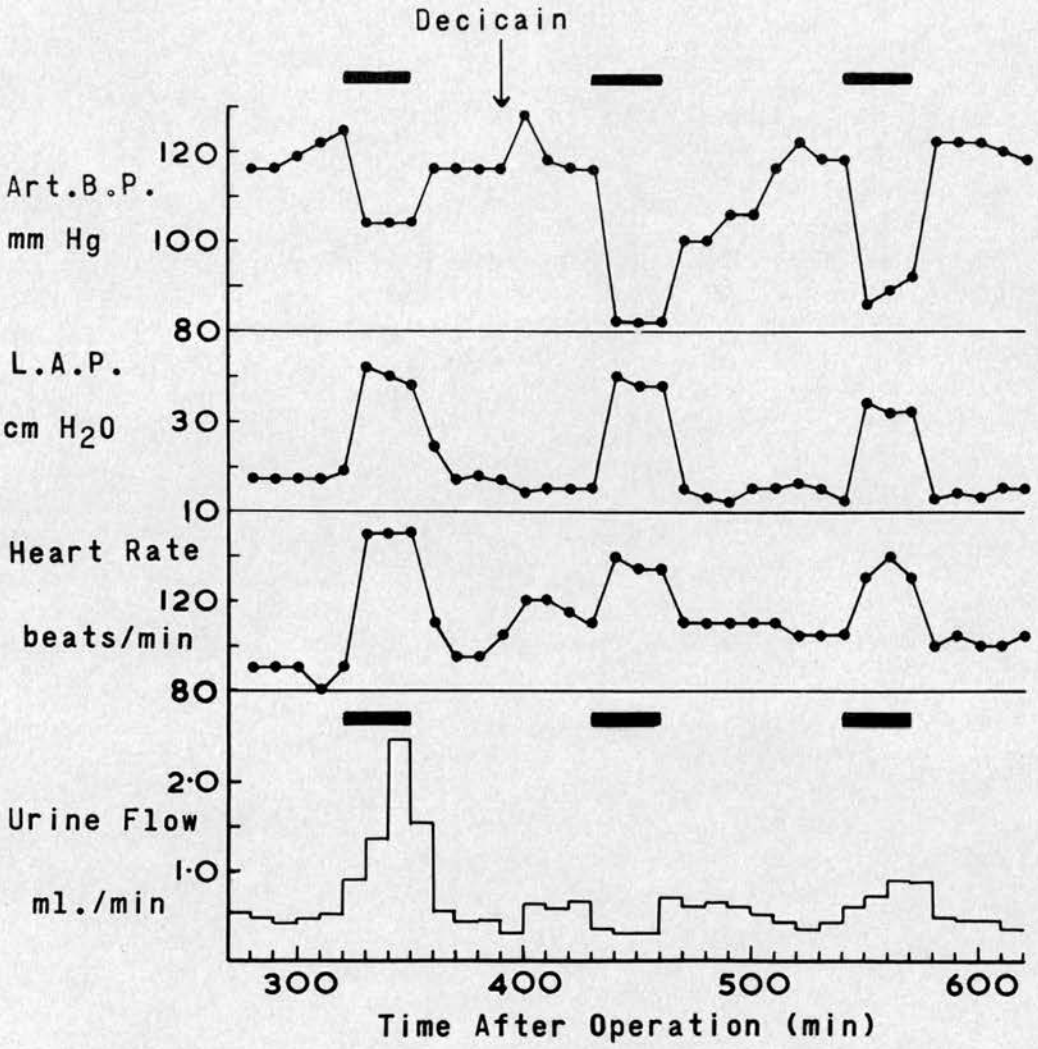

Fig.17. Effect of injecting a local anaesthetic into the pericardial cavity. From above downwards, femoral arterial pressure, left atrial pressure, heart rate and urine flow. Balloon inflated in left atrium in periods indicated by solid bars. Decicain 2% injected into pericardial cavity at time indicated.

comparable with inflations made without any local anaesthetic. The increases in heart rate were however always less when inflation was made after injection of amethocaine. Thus in the six control inflations in the same dogs heart rate increased by an average of 45 beats/min whilst after amethocaine the average increase was only 17 beats/min; the mean control rates were similar with and without amethocaine. As the injection of amethocaine affected respiratory movements the last of the three experiments was carried out with the chest open and artificial respiration maintained constant throughout; the result was similar to those in the other experiments in which respiration was spontaneous.

In one experiment methylene blue dye was added to the amethocaine hydrochloride solution and at post-mortem it was found to have spread throughout the pericardial cavity but was especially concentrated around the intrapericardial portions of the pulmonary veins. Since the phrenic nerves were paralysed the effects of the local anaesthetic were not localized to intrapericardial structures and the changes in the heart rate and urine flow response to atrial balloon inflation cannot be attributed only to the anaesthetization of sensory nerve endings in the left atrium. However these results do provide indirect evidence that the diuresis and possibly some cardio-acceleration that occurs when a balloon is inflated in the left atrium are dependant upon the integrity of nervous pathways in the thorax.

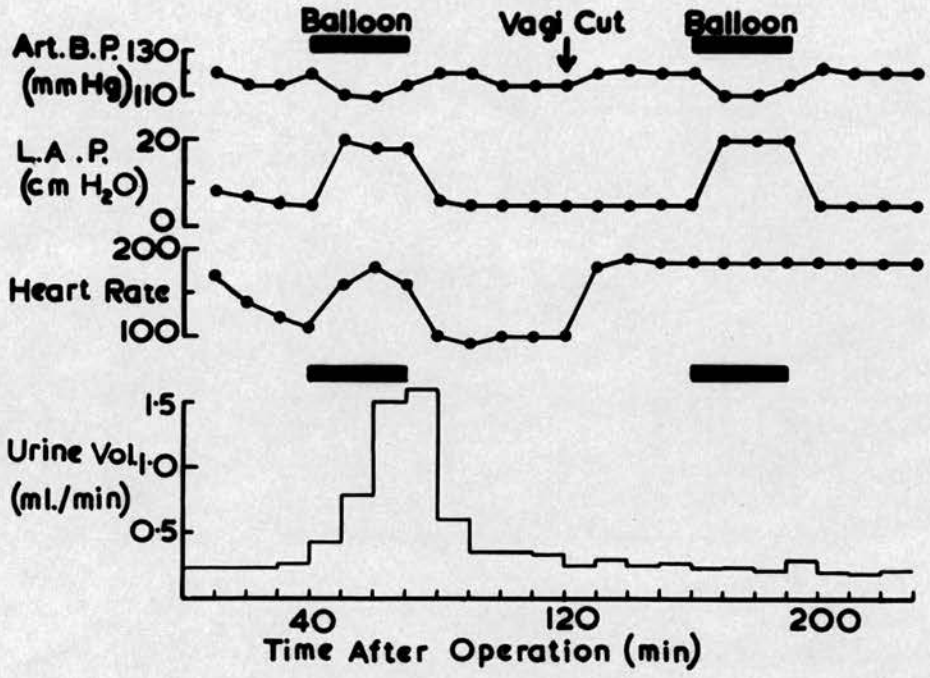

Fig.18. The effect of balloon inflation before and after cutting the vagus nerves. From above downwards, femoral arterial pressure, left atrial pressure, heart rate and urine flow. In this animal the chest was open and positive pressure artificial ventilation was maintained unchanged throughout. Vagi cut at time marked by arrow.

6. THE EFFECTS OF VAGOTOMY.

The vagus nerves were cut in the neck in five experiments. This usually caused an increase in heart rate and a rise in mean arterial pressure of about 5 mm Hg; left atrial pressure was unchanged and respiration became slow and increased in depth. In two experiments urine flow gradually increased after vagotomy by 50-100%, reached a peak after about 40 min and then decreased again to about its former level. During this increase in urine flow the concentrations of sodium and potassium remained constant so that the excretion of these substances increased. A similar small increase in sodium and potassium excretion after vagotomy was described by Pearce (1959).

In eight tests in five dogs a balloon was inflated in the left atrium after cutting the vagus nerves and no diuresis resulted in any of these tests; one experiment is shown in Fig.18. In five tests there was a small fall in urine flow on balloon inflation. The balloon was inflated at times varying from 40 minutes to 4 hours after vagotomy; in two experiments the vagus nerves were cut immediately after the operation whereas in three a typical diuresis was elicited by a test inflation before the vagus nerves were cut. When the dog was breathing spontaneously vagotomy caused changes in the rate and depth of respiration; in Fig.18 the dog received positive pressure artificial respiration maintained unchanged throughout. In this figure heart rate did not change when the balloon was inflated but in four inflations after vagotomy there was a small increase of about 10 beats/min on balloon inflation. Changes in left atrial pressure

and mean arterial pressure were similar to those seen during tests before vagotomy. Urinary sodium and potassium concentrations remained constant during balloon inflation after vagotomy.

CHAPTER II

OTHER TECHNIQUES USED TO PRODUCE DIURESIS IN ANAESTHETIZED DOGS.

A. THE EFFECTS OF DISTENDING THE INTRAPERICARDIAL PORTIONS OF THE PULMONARY VEINS.

The work reviewed in Part I of this report indicated that the stretch receptors in the left atrium are situated mainly in the intrapericardial portions of the pulmonary veins and the posterior wall of the left atrium. A method of stretching this portion of the atrium was therefore devised which it was hoped would not obstruct the flow of blood through the atrium.

1. EFFECTS ON URINE FLOW.

(a) METHODS.

The experiments were carried out using the same anaesthetic and preliminary preparation as in the previous series. The femoral vessels and both ureters were cannulated and the chest opened in the fifth intercostal space. The left lung was carefully retracted laterally and the pulmonary veins freed from their attachments. In the dog there are, on the left side, a single large upper and single middle pulmonary vein but the lower vein usually has two large branches which meet as the vein enters the pericardium. The lower of these two veins was tied off, as were any large branches of the other veins. Two ligatures were then passed around each vein and after collapsing the lung by gentle pressure the most peripheral of the ligatures were tied close to

the lung parenchyma. The other ligatures were pulled anteriorly as close to the pericardium as possible thus preventing reflux of blood from the atrium into a segment of the pulmonary veins. This usually left about 1 cm of vein free between the ligatures, the vein was then incised and a small balloon passed into the vein and pushed down beyond the second ligature. This ligature was tied so that less than 1 cm of the balloon projected beyond the ligature into the intrapericardial portion of the pulmonary vein. In this way a small balloon was placed in each of the three pulmonary veins on the left side of the left atrium. The balloons were made by tying finger cots over the end of 1 mm bore nylon tubing, the proximal ligature on the pulmonary vein forming the base of the balloon. When the surgical procedures were finished the distal ends of the nylon tubes were clamped so that the balloons could not pull into the atrium when they were inflated. When the balloons were in position a soft string was placed around the root of the left lung and tied tightly immediately posterior to the cannulated veins, thus occluding all structures in the lung root.

A metal cannula was inserted into the left atrium through the appendage and clamped to allow a recording of left atrial pressure. Left atrial pressure and femoral arterial pressure were recorded using Statham P23 G strain gauges operating mirror galvanometers writing directly on photographic paper sensitive to ultra-violet light. The frequency response of each system was at least flat to 60 c/s $\pm$ 5%. This is adequate to record blood pressure at

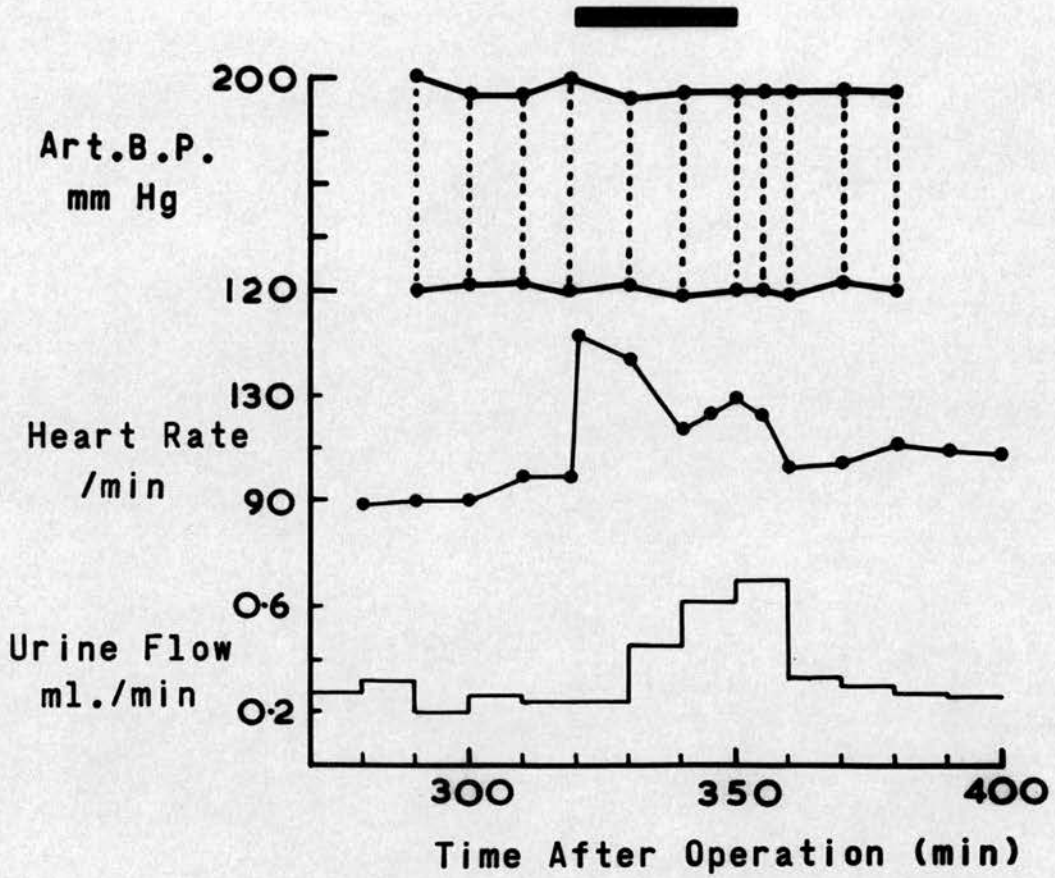

Fig.19. The effect of inflating balloons in the left pulmonary veins. From above downwards, systolic and diastolic arterial pressure, heart rate and urine flow. 3 ml. 0.9% Na Cl injected into each balloon during 30 min indicated by the solid bar.

heart rates up to 360 beats/minute.

The chest was left open and positive pressure artificial respiration maintained throughout the experiment. No blood or other infusion was given during these experiments except the 0.6% sodium chloride solution in which the anaesthetic was administered.

(b). RESULTS.

Six dogs were used in these experiments. Balloons in the pulmonary veins were inflated by injecting 3 ml. 0.9% sodium chloride solution at 38°C into each balloon; the balloons were kept inflated for 30 min and then deflated. Two dogs responded to this manoeuvre with an increase in urine flow similar in time course and magnitude to the changes in urine flow produced by obstructing the mitral orifice. In the other four dogs the changes in urine flow were indistinguishable from small spontaneous variations occurring during the control periods. Figure 19 shows the largest change in urine flow produced by this procedure.

It had been hoped that inflating these balloons would not be accompanied by any cardiovascular changes and that if changes in urine flow then occurred they could be regarded as independent of any cardiovascular change. However Fig.19 shows that distending the balloons in the pulmonary veins produced an increase in heart rate which was maintained whilst the balloons were inflated and although the rate fluctuated during the thirty minute period it decreased again 2-5 minutes after the balloons were deflated. Mean arterial blood pressure was little affected by the procedure and

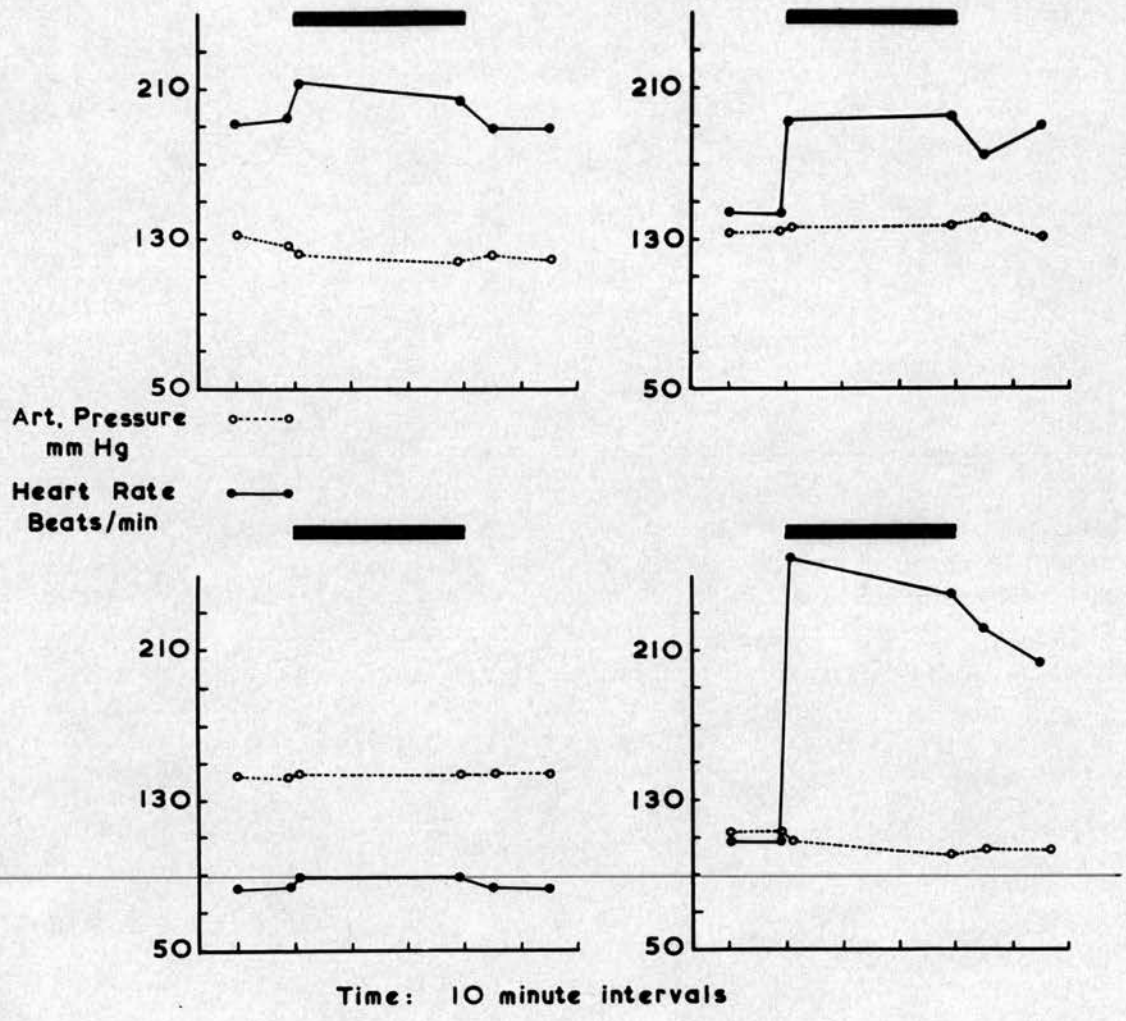

Fig.20. The effects of inflating balloons in the left pulmonary veins in four dogs. On the ordinates, mean arterial pressure (interrupted line) and heart rate (continuous line). Balloons inflated during the 30 min periods indicated by the solid bars.

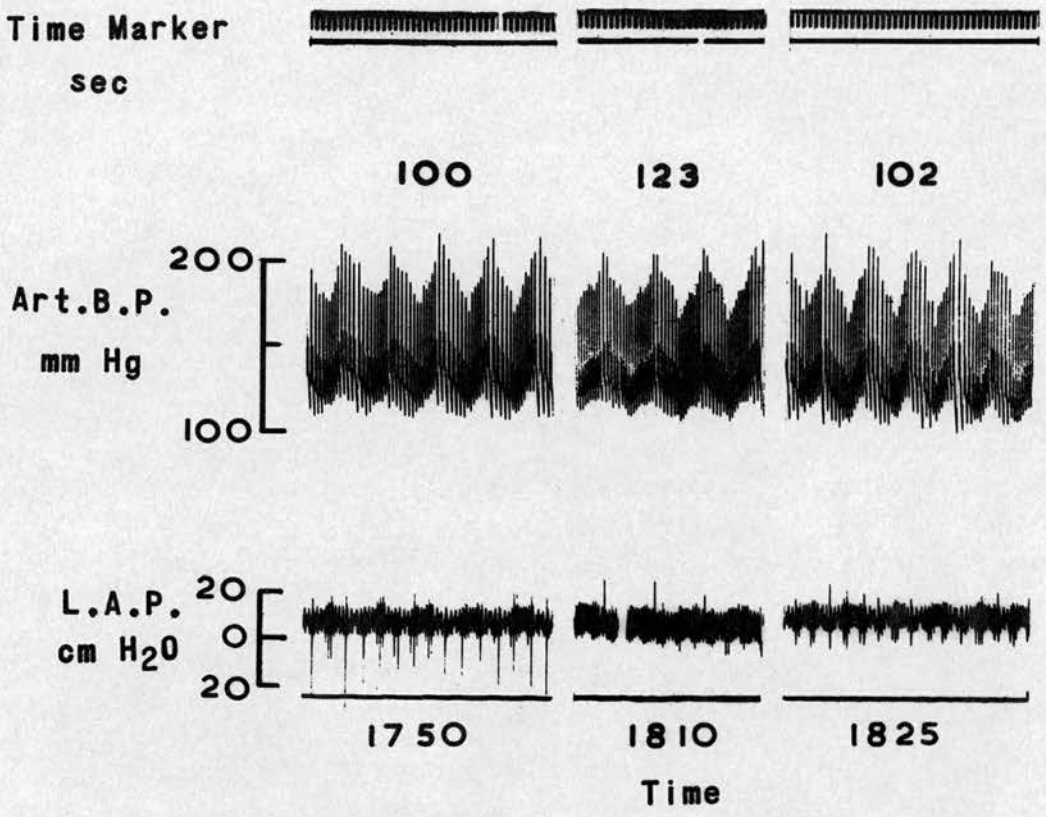

Fig. 21. The effect of inflating balloons in three left pulmonary veins. 3ml. saline injected into each balloon at 1751 and removed at 1820. Heart rate written above arterial pressure record.

fell gradually during the experiment. On each of eight occasions when the balloons in the pulmonary veins were inflated the heart rate immediately increased. The mean heart rate before inflation was 140/min and increased by an average of 25% during inflation. The average mean blood pressure, estimated as mean diastolic pressure plus one-third of the pulse pressure, decreased by 3 mm Hg from 126 mm Hg before inflation. However in three inflations blood pressure increased, and no correlation could be established between the changes in blood pressure and heart rate. Figure 20 shows the changes in heart rate and the changes in blood pressure in each of four inflations. There was no change in mean atrial pressure in any of these experiments. A sample of the record from the experiment illustrated in Fig.19 is shown in Fig.21. Twenty minutes after inflation of the balloons heart rate was 20% higher than before inflation and mean blood pressure was unchanged although pulse pressure was decreased. Five minutes after deflation of the balloons the heart rate wassimilar to that before inflation although mean arterial pressure had been gradually falling.

Although inflating balloons in the pulmonary veins did sometimes produce an increase in urine flow this did not appear as frequently as in the experiments in which the mitral opening was obstructed. However placing balloons in the pulmonary veins did mean that one lung was non-functioning and if in fact stimulation of left atrial receptors is an essential part of the diuretic response then only half of these receptors would be stimulated by this procedure. Inflating the balloons in the pulmonary veins

caused changes in heart rate and pulse pressure and the possibility that the diuresis is secondary to altered renal haemodynamics was therefore not eliminated. The lack of any relationship between changes in heart rate and blood pressure had also been noted in some of the previous experiments when the circulation was obstructed and these changes were therefore examined in more detail in another series of experiments.

2. CARDIOVASCULAR EFFECTS.

(a) METHODS.

Eight dogs of 12 - 15 kg were used in these experiments and balloons were placed in each of three pulmonary veins as already described. One additional procedure was made: each animal received 50 ml. of heparinized dog blood immediately after induction of anaesthesia and then another 50 ml. was given slowly over the next 20 minutes. When the chest was opened another 50 ml. of blood was infused slowly so that each dog received 150 ml. blood during the operative procedures. It was hoped in this way to prevent or minimise the progressive metabolic acidosis liable to occur in animals anaesthetized and depleted of their blood volume, The maintenance of the blood volume also resulted in the animals having a slower heart rate after the operation than in the previous experiments. However three of the eight experiments had to be abandoned as these animals were found to have pulsus alternans and heart rates of over 200 beats/min when the chest was opened. As clipping the carotid arteries in these animals had little or no effect on the heart rate it was not considered worth while attempting

DOG NO.	VOL.EACH BALLOON ml.	HEART RATE BEATS/MIN			SYSTOLIC PRESSURE mm Hg			DIASTOLIC PRESSURE mm Hg		
		B.	D.	A.	B.	D.	A	B.	D.	A
40	3	90	120	90	198	186	181	119	123	123
41	3	81	93	90	177	180	177	78	87	84
45	3	168	216	186	147	145	148	87	88	88
46(a)	1	111	122	112	130	130	130	95	95	90
(b)	2	110	130	135	130	128	128	95	90	90
(c)	3	96	129	111	138	133	130	95	95	95
48(a)	3	51	123	54	200	200	200	130	145	135
(b)	2	54	95	54	205	198	200	140	143	140
(c)	1	53	123	59	190	185	185	125	125	130
49 (a)	2	108	162	123	175	155	155	110	110	105
(b)	1	105	140	120	170	160	160	105	100	100
51 (a)	0.5	69	72	67	160	165	165	110	110	110
(b)	1	67	75	73	165	165	165	110	115	115
(c)	1.5	73	78	72	165	165	165	115	115	115
(d)	2	72	81	72	170	165	165	110	110	110
(e)	3	66	72	69	165	155	155	110	115	115
(f)	1	48	51	51	135	135	135	90	90	90
(g)	2	48	59	54	155	155	155	95	100	95
(h)	2	45	49	45	155	155	150	95	100	95
(i)	3	45	57	48	150	150	145	90	100	90
(j)	1	41	45	39	150	150	145	90	95	90
(k)	2	39	46	43	147	145	143	90	95	90
(l)	3	43	54	44	147	150	145	90	105	95
(m)	2	42	55	53	150	150	145	90	95	90
52 (a)	2	66	93	72	140	137	135	90	95	90
(b)	2	60	81	67	145	142	140	90	95	85
(c)	2	67	81	66	135	130	130	85	85	85
(d)	3	48	60	51	130	140	130	85	95	85
(e)	3	51	81	51	135	140	135	90	100	90
(f)	3	51	63	51	130	135	130	85	95	85
MEANS.		66	88	74	158	154	153	100	107	100

Table 6. The effects of inflating balloons in the left pulmonary veins. Thirty inflations each lasting 0.5 - 3 min. Heart rate, systolic pressure and diastolic pressure before (B) during (D) and 2 min after (A) inflation of balloons.

to examine the effects of distending the pulmonary veins. The cause of the high incidence of pulsus alternans in this series is not clear; the only difference between this and the other series was the infusion of blood these animals received.

The balloons were distended at each test by 1, 2 or 3 ml. of 0.9% sodium chloride solution warmed to 38°C; the balloons were distended for 0.5 to 3 min and then deflated. Left atrial pressure and femoral arterial pressure was recorded from capacitance manometers operating ink writers (flat to 20 c/s ± 5%). Mean systemic arterial pressure was calculated as diastolic pressure plus one third of the pulse pressure.

(b) RESULTS.

Twenty-seven inflations of the balloons in the pulmonary veins were made in five dogs. In addition a short inflation was made in each of three dogs in the preceding section when recording was made using mirror galvanometers, and these results are included here. In every one of the thirty inflations heart rate increased (Table 6). The mean heart rate before inflation was 66 beats/min and the average increase 28% (S.E.M. ± 7.2); the cardio-acceleration occurred immediately the balloons were inflated and fell to control levels about 0.5 to 1 min after deflation of the balloons. In eight inflations mean arterial blood pressure fell; in three it was unaltered and in nineteen it increased; the average change in blood pressure was an increase of 2.5 mm Hg. The most usual change in blood pressure was a decrease in systolic pressure and an increase in diastolic pressure so that

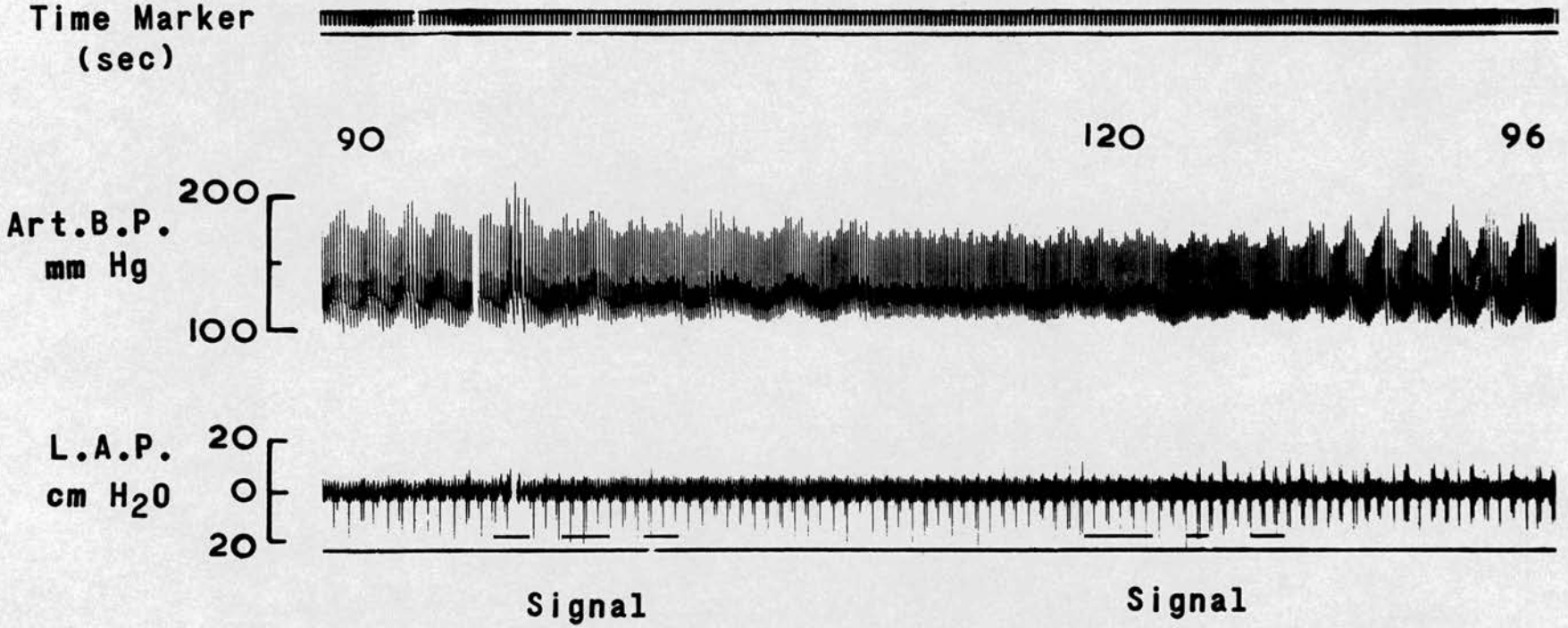

Fig.22. The effect of inflating balloons in three left pulmonary veins.At the first signal 3ml. saline injected into each balloon and at the second signal the saline was removed. Heart rate written above arterial pressure record.

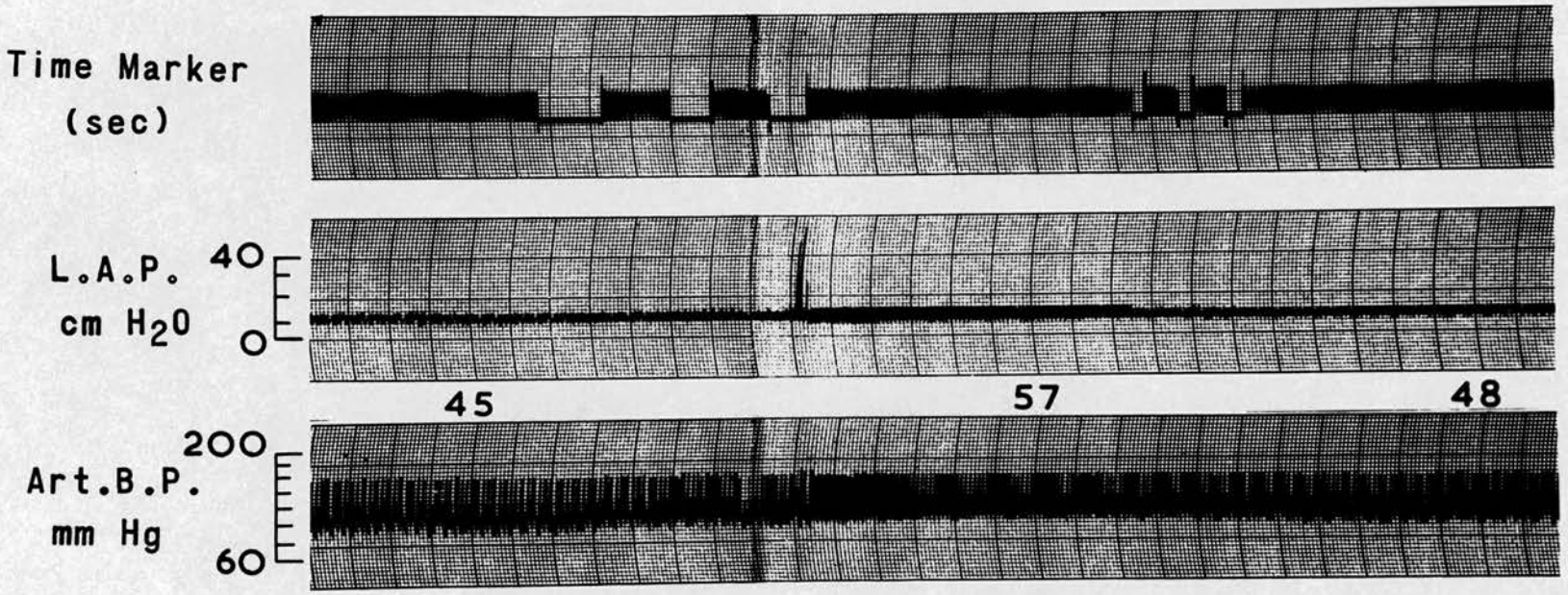

Fig.23. The effect of inflating balloons in three left pulmonary veins. At the first signal 3ml. saline injected into each balloon and at the second signal the saline was removed. Heart rate written above arterial pressure record.

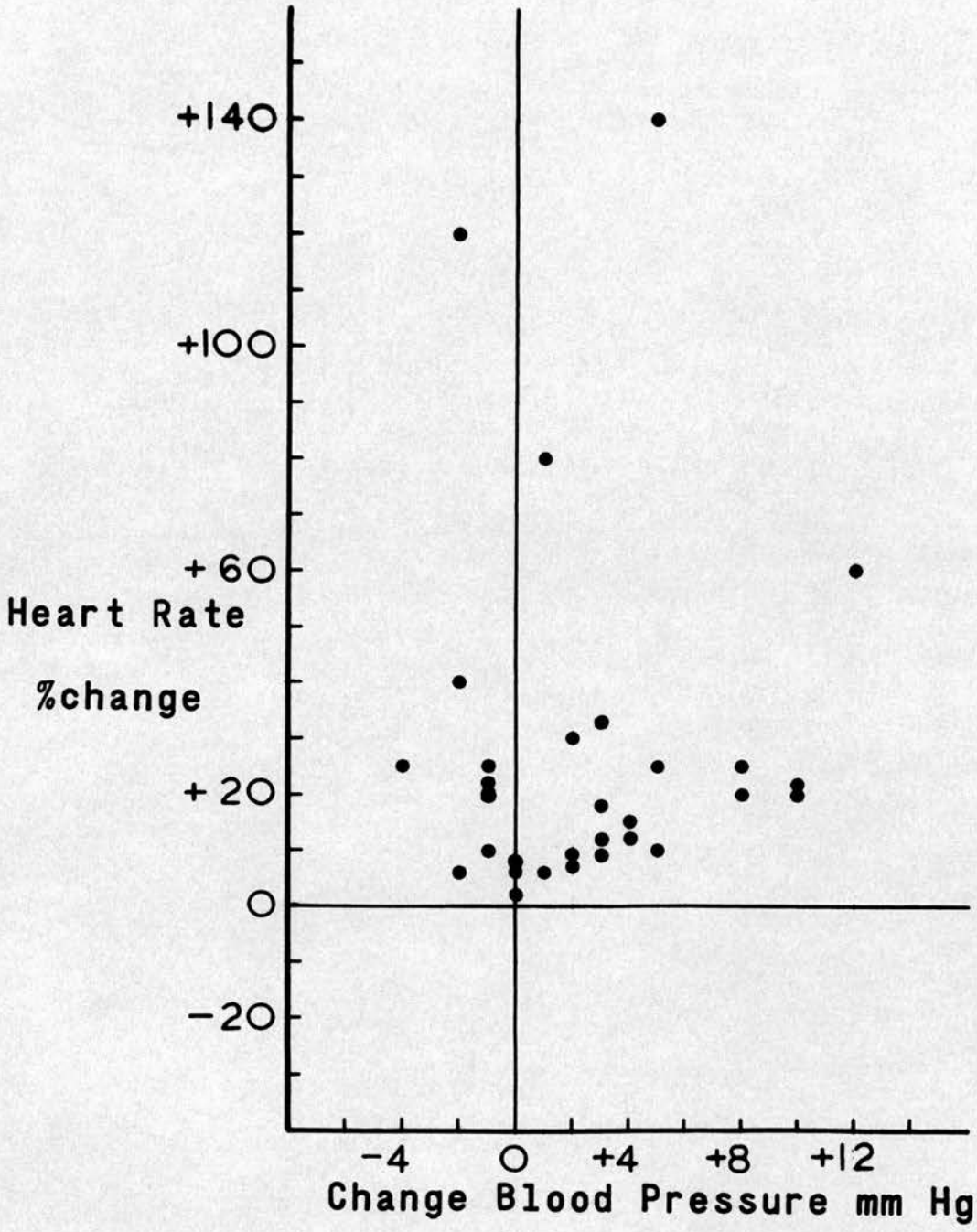

Fig.24. The effects of inflating balloons in the left pulmonary veins. Thirty inflations in eight dogs. Percentage change in heart rate compared with the change in mean arterial pressure.

although pulse pressure was reduced mean pressure showed little change. This effect is shown in Fig.22 which was recorded using a mirror galvanometer. Figure 23 recorded using ink writers shows an experiment in which there was a marked increase in diastolic pressure and also a moderate increase in heart rate. It may be seen from these records that heart rate decreased rapidly after deflation whereas previously when the balloons were inflated for half an hour it took 2 - 5 min before the heart rate returned to its preinflation level. No relationship could be established between the changes in heart rate and the changes in blood pressure, and both heart rate and blood pressure often increased (Fig.24). Mean left atrial pressure did not change by more than $\pm$ 1 cm water during any inflation although the record sometimes showed greater oscillations in this period.

B. THE EFFECT OF INCREASING THE HEART RATE.

Two methods of producing diuresis in anaesthetized dogs have been described so far. The most striking cardiovascular change caused by both obstruction of the mitral orifice and distension of the pulmonary veins was an increased heart rate. The effect on the urine flow of artificially increasing the heart rate was therefore tested.

Two silver electrodes were sewn to the left atrial appendage of a dog prepared as for the previous experiments. A square wave stimulus was applied of strength 2 volts and duration 5m sec at a rate faster than the resting heart rate. Five tests were made in

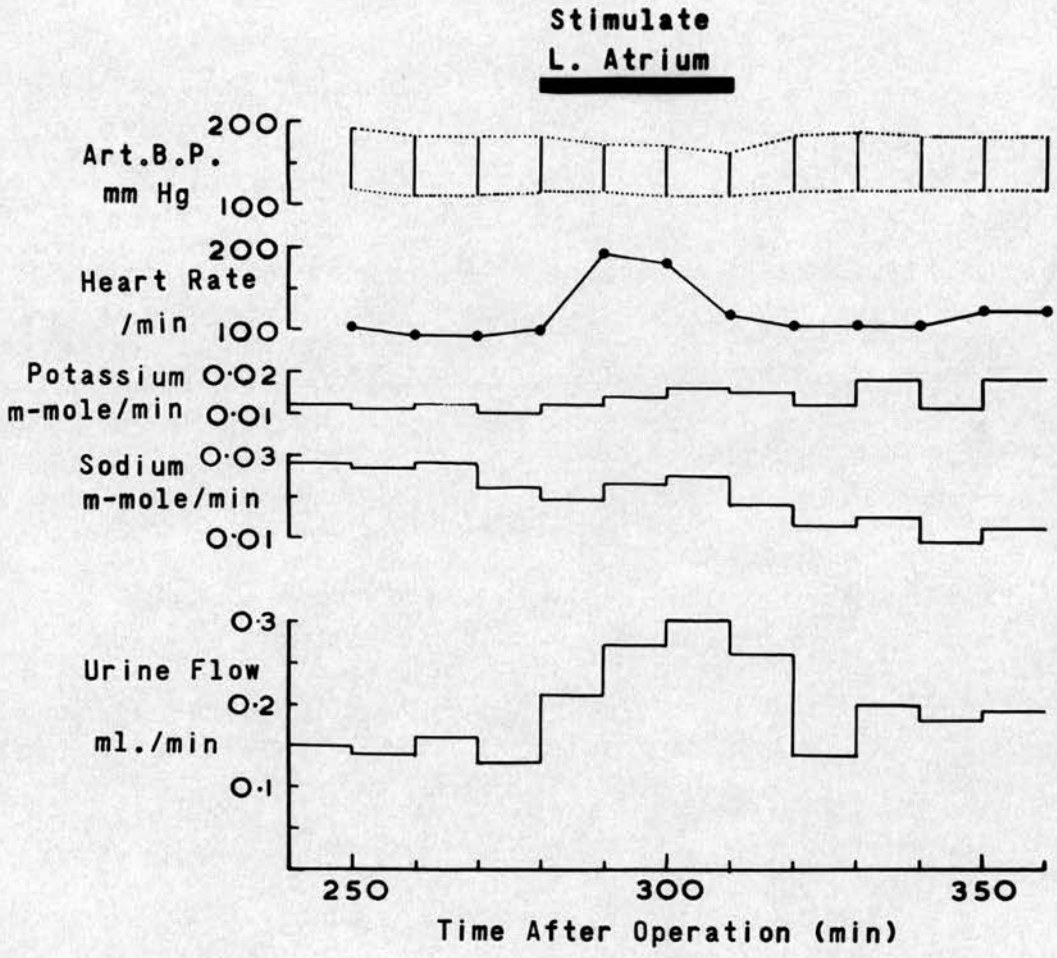

Fig.25. The effect of increasing the heart rate by stimulating the left atrial appendage. From above downwards, femoral arterial pressure, heart rate, potassium excretion, sodium excretion and urine flow.

two dogs and the heart rate was increased on each occasion for half an hour; there was a small increase in urine flow during the period of stimulation in each test. Figure 25 shows the result of one of these experiments; the heart rate was increased from 100 to 180 beats/min but the heart slowed gradually in spite of the continued stimulation, there was a decrease in pulse pressure but little change in mean arterial pressure whilst the heart rate was increased. Urine flow doubled and the urine became more dilute so that the excretion of sodium and potassium remained relatively constant. Thus this small diuresis resembled that produced by obstructing the mitral orifice.

PART III

DISCUSSION.

CHAPTER I

THE EFFECTS OF LEFT ATRIAL DISTENSION.

A. LEFT ATRIAL DISTENSION AND DIURESIS.

1. INTRODUCTION.

The main experimental finding of Henry et al. (1956) has been confirmed; obstruction of the left atrium in dogs under chloralose anaesthesia produced an increased flow of urine. The diuresis was transient and small when compared to water diuresis in conscious dogs, but resembled a water diuresis in its time course and in the fact that the urine became more dilute during the diuresis. It was never possible to predict from the heart and respiration rates, arterial and left atrial pressure recorded either before or during balloon inflation whether the effect of inflating the balloon would be comparatively large or virtually absent. Technical procedures mentioned by Henry et al. (1956) as likely to ensure a good response proved unreliable and no way was found of ensuring consistent responses. Similar transient increases in urine flow occurred spontaneously and in response to various other manoeuvres. However, despite the occasional spontaneous diuresis the results in Fig.7 were sufficient to establish that inflation of a balloon in the left atrium did produce a diuresis but explanations of the mechanisms involved remain largely speculative. An attempt has been made firstly to define the afferent mechanisms which produced the diuretic response and secondly to define the agent acting on the kidney to produce diuresis.

2. THE NATURE OF THE AFFERENT MECHANISM.

Henry et al. (1956) believed that the diuresis was the result of stimulation of stretch receptors in the left atrium basing their belief on their observations that tightening snares around the pulmonary veins or injecting emboli to block the pulmonary arteries did not produce diuresis. These two procedures were thought to produce similar effects to mitral obstruction with the exception that only the latter procedure distended the left atrium. In the experiments of Henry et al. (1956) the injection of plastic spheres of diameter 40-80 μ caused no change in respiration or systemic arterial pressure although pulmonary embolization usually provokes tachypnoea and dyspnoea and possibly changes in the pulmonary vascular system (reviewed by Whitteridge, 1950; Nelson & Smith, 1959). The technique used to snare the pulmonary veins meant that both sides of the chest had to be opened and then later one snare was pulled tight and the other closed gradually to produce an increase in pulmonary arterial pressure of about 20 cm water. On the evidence of Steinberg and Mundy (1936) this would require that about 70% of the pulmonary vascular bed should be blocked. Respiratory rate increased and there was a 30% increase in heart rate although systemic arterial pressure was said to be unaltered as was the cardiac output. In view of the unpredictable nature of the urinary response to mitral obstruction the fact that snaring the pulmonary veins and embolization of the lungs did not produce a diuresis cannot be regarded as proof of the hypothesis that atrial receptors form

the afferent limb of a reflex linking atrial distension with urine flow.

Inflation of a balloon in the left atrium produces distension of the left atrium, pulmonary vascular congestion, a rise in pulmonary arterial pressure, a fall in systemic arterial pressure, a change in pulse pressure and an increase in heart rate. Henry et al. (1956) found no change in systemic arterial pressure, and the results in Table 2 do not indicate that the diuresis was affected by the change in mean arterial pressure in the present series. An equally good diuresis was obtained on occasions when there was a fall of 20 mm Hg and when there was no change in arterial pressure. It might have been expected that in those animals in which the blood pressure was low or there was a marked fall in blood pressure the urinary response to balloon inflation would be reduced. There is no evidence that this was so, but if blood pressure fell very low, to about 60 mm Hg, urine flow ceased (Fig.16). In anaesthetized dogs renal plasma flow is well maintained at arterial pressures ranging from 150 - 100 mm Hg (Selkurt, Hall & Spencer, 1949) but at about 60 mm Hg urine flow usually ceases (Smith, 1951).

Right atrial pressure does not change during inflation of a balloon in the left atrium and therefore stimulation of receptors in the right atrium is not essential for the diuresis. However, Henry (1955) believed that had the experiments been designed to distend both atria a more marked diuresis would have resulted As indirect evidence for this conclusion he claimed that a good

diuretic response to balloon inflation could be obtained only after infusion of blood or plasma which should increase the volume of the right atrium. The effects of such infusions are more widespread, and it was not possible to confirm that infusions of blood or plasma did improve the response to balloon inflation. The design of experiments to affect right atrial receptors is difficult since lacking the right ventricle to provide a driving force, any obstruction to blood flow would cause pooling of blood in the peripheral circulation. However until such experiments can be designed there is no evidence that stimulation of receptors in the right atrium has any effect upon urine flow.

When balloons were distended in the intrapericardial portions of the left pulmonary veins there was sometimes a small diuresis similar to that produced by mitral obstruction. Although this procedure was unlikely to cause any obstruction to the circulation there was still a considerable increase in heart rate accompanied by small changes in mean systemic arterial pressure and an altered pulse pressure.

When the heart rate was increased by stimulating the left atrial appendage there was also an increase in urine flow which resembled that produced by mitral obstruction both in its time course and in the fact that the urine became more dilute. Such stimulation may possibly have affected receptors in the left atrium either directly or indirectly as a result of the increased number of atrial contractions per minute. This experiment does not show that the diuresis can be produced without stimulation of atrial receptors,

but may provide a method of studying the response more closely.

Cutting the vagus nerves abolishes the diuretic response to inflation of a balloon in the left atrium. But section of the vagi involves the interruption of many different efferent and afferent nerve fibres and cannot be regarded as merely interrupting the afferent limb of a specific reflex. Section of the vagi produces a very great disturbance of the circulation and respiration and the absence of the diuresis might be due to such general effects rather than the loss of impulses from intrathoracic receptors. Since the circumstances under which the response appeared could not be defined it is impossible to say whether the general state of the animal after vagotomy was or was not such that a diuresis should be expected.

The inhibition of the diuretic response to balloon inflation by the injection of local anaesthetic into the pericardial cavity also suggests that nervous pathways within the thorax are an essential part of the mechanism producing diuresis. However, the inability to define the limits of diffusion of the anaesthetic agent and the impossibility of defining the general state of the animal prevents a more precise conclusion.

No conclusion can therefore be reached as to the afferent mechanism by which diuresis is produced when the mitral orifice is obstructed or the pulmonary veins are distended, nor can it be stated that stimulation of left atrial receptors is an essential part of the mechanism.

3. AGENTS ACTING ON THE KIDNEYS.

(a) INTRODUCTION.

Whether the mechanism producing diuresis is a reflex with its afferent fibres in the vagi or the diuresis is produced by some other mechanism, some agent must eventually reach and act on the kidney to produce the increase in urine flow. However, before attempting a detailed discussion it should be pointed out that the diuresis in the experiments reported in this work was small, transient and in animals under chloralose anaesthesia. The urinary effects of agents known to act on the kidneys (O'Connor, 1962) have been described from experiments in which large effects persist in conscious animals; comparison between the two types of experiments may be misleading.

(b). VASOPRESSIN.

Henry et al. (1956) carried out their experiments on atrial distension because study of the effects of negative pressure breathing in dogs and humans had convinced them that stimulation of intrathoracic receptors did produce inhibition of the neurohypophysis, and so diuresis; their object was to determine the site of the receptors. Procedures were therefore adopted which it was thought would reduce the rate of release of antidiuretic hormone from the neurohypophysis. The animal's chest was closed and spontaneous respiration was restored, then four to six hours elapsed before testing the effect of inflating a balloon in the left atrium. This it was believed "gave time for a decrease in the level of antidiuretic hormone

secretion which Eisen & Lewis (1954) have shown may be greatly increased for a few hours following an operation". The appearance of the diuresis under these conditions has undoubtedly been regarded as circumstantial evidence that the diuresis did depend upon changes in antidiuretic hormone release. It has been possible to show that it is not necessary to close the chest or to wait for four to six hours after the operation to obtain a diuretic response to mitral obstruction.

The effects of a decrease in the release of antidiuretic hormone from the neurohypophysis may be seen in conscious animals following ingestion of water, or in diabetes insipidus. If 400 ml. of water is given to a conscious dog by stomach tube urine flow rises to a maximum of about 6 ml./min after a delay of about 40 - 60 min (Fig.11). Klisiecki, Pickford, Rothschild & Verney (1933) established that alimentary absorption occurred well in advance of the diuresis and showed in their experiments in the dog there was an interval of 15 min between the peak of the water load and the peak of the diuresis. This latent period may be attributed to the gradual destruction of that diuretic hormone already released from the neurohypophysis. In the absence of antidiuretic hormone release urine flow increases as a result of a decreased reabsorption of water and urinary solute concentration falls so that there is little or no change in solute excretion. Thus the diuretic response to inflation of a balloon in the left atrium resembles a small water diuresis in that it appears about fifteen minutes after the stimulus is applied, and is not accompanied

by a change in solute excretion. The diuretic response to mitral obstruction has therefore been attributed by many authors to a decreased release of antidiuretic hormone from the neurohypophysis (Smith, 1957; Neil, 1960).

Water diuresis may be inhibited in the conscious dog by intravenous injection of 1 m-u. of posterior pituitary extract (O'Connor & Verney, 1942). Following such injections maximum inhibition is reached ten minutes after the injection and then recovery occurs. Water diuresis may be inhibited in the conscious dog by intravenous infusion of posterior pituitary extract at a rate of about 0.07 m-u./min (Verney, 1947). With infusions at this rate maximum inhibition occurs after the infusion has been running for about thirty minutes. Shannon's (1942,b) experiments on replacement therapy in dogs with diabetes insipidus showed that antidiuresis could be obtained with infusions of posterior lobe extract 1-5 m-u./hr and minimal urine flows were usually obtained with the upper limit of this range. In the experiments described in this report infusion at a rate of 0.009 m-u./kg/min was necessary to inhibit completely water diuresis in a conscious dog, that is, about double the previous figures, but the extracts used contained a mixture of lysine vasopressin and arginine vasopressin.

Many anaesthetic agents appear to have an inhibitory effect on water diuresis (reviewed by Pickford, 1945), but Smith (1951) has stated that uncomplicated water diuresis may occur during chloralose anaesthesia. Theobald (1934) gave to dogs by stomach

tube anaesthetic doses of chloralose dissolved in 300 ml. water. The animals "fell asleep" during the course of the water diuresis and this diuresis, which was uninterrupted, could be inhibited by the same doses of vasopressin that inhibited water diuresis in a conscious animal. However, even a small afferent stimulus such as shaving the hair produced inhibition of the diuresis. de Bodo & Block (1941) gave a loading dose of water 40 minutes before inducing anaesthesia with chloralose so that the dog became anaesthetized during a water diuresis; under these circumstances the water diuresis continued. The conditions during the present series of experiments were very different in that a diuresis was induced by inflation of a balloon in the left atrium of an animal anaesthetized for at least three hours and having undergone a major surgical operation.

Injection of morphine intravenously in doses of 0.03 mg/kg into conscious dogs will inhibit water diuresis by causing release of antidiuretic hormone (Duke, Pickford & Watt, 1951). It is possible that at least in human subjects larger doses may affect glomerular filtration rate (Papper, Saxon, Burg, Siefer & Rosenbaum, 1957). The dogs in the experiments described here were all given 15 mg morphine sulphate subcutaneously as a preoperative sedative at least four hours before any experimental tests were made. But Henry (1955) gave additional doses of 0.5 mg/kg/hr morphine sulphate if the resting rate of urine flow rose above 0.5 - 1 ml./min but does not state whether this was given intravenously or subcutaneously.

If such injections do prevent spontaneous variations in urine flow in these animals this may be due to the sedative action of morphine which produces an animal showing much less muscular movement and a more constant heart rate and blood pressure than the animal without morphine, rather than an inhibition of diuresis dependant upon an additional release of antidiuretic hormone.

Eisen & Lewis (1954) showed that the release of antidiuretic hormone was elevated for 6-12 hours and sometimes 24 hours after a surgical operation on human subjects. Haemorrhage may also induce a massive release of antidiuretic hormone (Ginsburg & Brown, 1957). It is therefore likely that at the time a balloon was inflated in the left atrium of the dogs in the present series that there was a relatively rapid release of antidiuretic hormone from the neurohypophysis. Under conditions similar to these Verney (1929) found that water was absorbed from the stomach but no diuresis resulted. In the present series, water was absorbed from the stomach but only excreted comparatively slowly and it could not be established that injections or infusions of vasopressin in doses adequate to inhibit water diuresis in conscious dogs in any way affected this slow excretion of water. Verney (1929) noted that although the maximum urine flow following hypophysectomy in anaesthetized dogs is usually much less than in diabetes insipidus, or in water diuresis in the conscious animal, the amount of intravenously infused post-pituitary antidiuretic substance needed to bring the urine flow back to and maintain it at its previous rate is much greater. Thus in hypophysectomized anaesthetized dogs

about 70 μ-u./sec was needed to inhibit the diuresis compared with 1 μ-u./sec for antidiuresis in conscious animals (Verney, 1954). It is not clear whether true water diuresis fails to occur in these traumatized anaesthetized animals because of a continuous release of antidiuretic hormone or some other substance or because of a defect in the kidney itself. Chloralose in conjugated form is excreted in the urine (Kochmann, 1923) and may well affect the tubular cells; the urine in the present experiments contained a reducing substance that did not give the colour changes characteristic of glucose with Benedict's quantitative reagent. Permutt[1] (1961) has recently examined the renal activity of vasopressin in traumatized, pentobarbital anaesthetized dogs. To induce a diuresis an infusion of 5% dextrose in water 5 ml./min was given for about four hours and vasopressin then infused. By this time urine flow had reached about 5 ml./min and infusion of 50-100 m-u./hr vasopressin caused a decrease in urine flow and an increase in sodium excretion, changes which were reversed when the infusion stopped. Infusion of vasopressin at a rate of 25 m-u./hr sometimes caused a decrease in urine flow whilst smaller doses did not affect urine flow but did increase sodium excretion. However, even doses of 50-100 m-u./hr did not produce full inhibition of urine flow which fell only to 1-2 ml./min. It cannot be decided from these experiments whether or not the effects of vasopressin are the result of a direct action on the renal cells or secondary to some haemodynamic change. It is however apparent that doses of vasopressin more than adequate to

inhibit water diuresis in conscious animals have little effect on urine flow in these anaesthetized animals in which diuresis was induced by excessive hydration. Doses of vasopressin not much above the antidiuretic range may have vascular actions. In rats a dose of about one hundred times the antidiuretic dose will produce pressor effects (Thorn, 1958) and in dogs doses of 10-50 m-u. may produce coronary constriction, lasting for 30 min (Bulbring, Burn & Walker, 1949).

Verney (1954) recognised that the appearance of water diuresis was dependent on an adequate primary supply of glomerular fluid and considered that the failure of polyuria to appear in one third of his dogs after hypophysectomy (Verney, 1929) could be attributed to this fact. In these dogs when polyuria appeared it was always more profuse on the side on which the nerve supply to the kidney had been removed. Bayliss & Fee (1930) were unable to produce a polyuria in any neurohypophysectomized anaesthetized dogs until the kidney had been denervated. When they perfused a kidney in situ from a heart-lung preparation polyuria supervened only when the kidney was denervated. and this procedure was followed by an increase in renal blood flow. The polyuria was inhibited by the addition of a large dose of vasopressin to the preparation but this also reduced renal blood flow. Verney's (1926) results also indicate that in the perfused isolated kidney there may be a marked reduction in renal blood flow as well as antidiuresis when posterior pituitary extracts are injected (Fig.8 of his paper).

An inhibition of urine flow was also induced when the perfusing blood was circulated through a dog's head but it is possible that such a procedure could lead to the addition to the blood of amounts of vasopressin well in excess of the normal physiological antidiuretic dose. The results of Shannon (1942a) are of interest as he studied the control of the renal excretion of water in four dogs who had chronic diabetes insipidus for at least a year before the experiments. There was a rough correlation between the state of hydration and water excretion and during dehydration the urine was hypertonic. When these dogs ingested saline there was an increase in inulin and creatinine clearances and an increase in urine flow which was not at first accompanied by an equivalent increase in the excretion of sodium. This initial dilute diuresis resembles that seen in well hydrated normal dogs (O'Connor, 1955) although in the latter sodium excretion increases more rapidly. Shannon (1942a) regarded changes in glomerular filtration as an important regulating mechanism in diabetic animals although there is a possibility that neurohypophysial remnants may play some part.

It is likely that although a decrease in the level of antidiuretic hormone is the primary pre-requisite for the appearance of water diuresis the size and time course of the diuresis may be modified by changes in renal blood flow and by agents causing changes in glomerular filtration. Berliner & Davidson (1957) using a conscious dog found that inflating a cuff round one renal artery during a water diuresis caused a

reduction in urine flow but a smaller fall in solute excretion so that the urine became more concentrated and was on occasions hypertonic to plasma. Water diuresis was uninterrupted in the other kidney so that the urine concentration was not due to a release of endogenous vasopressin. In anaesthetized dogs in which a dilute diuresis had been induced, del Greco & de Wardener (1956) showed that a decrease in renal blood flow produced by occlusion of the aorta or inhalation of cyclopropane resulted in a decreased urine flow and a more concentrated urine. In these dogs 100 m-u. vasopressin injected intravenously had no effect on urine flow. Water diuresis in conscious dogs may be inhibited by vasoactive substances such as adrenaline, thus O'Connor & Verney (1945) showed an inhibition of water diuresis by an intravenous injection of 40 µg adrenaline. O'Connor (1958b) later showed that an infusion of adrenaline during the rising phase of water diuresis produced a slowing of the diuresis. Adrenaline infused at a rate of 0.1 - 0.2 µg/kg/min halved the rate of urine flow but was also sufficient to cause changes in the cardiovascular system (Holgate & O'Connor, 1958). There was no evidence that this inhibition of water diuresis was due to a liberation of neurohypophysial hormone by adrenaline. Arterial blood pressure may be increased by about 40 mm Hg in conscious dogs by occluding the carotid arteries. If this is done in dogs prehydrated with saline to ensure adequate glomerular filtration then there is an increase in urine flow with little or no change in sodium concentration (O'Connor, 1958a).

When the carotid arteries are clamped during the rising phase of water diuresis there is also an increase in urine flow.

From these observations it seems possible that the kidneys in a traumatized anaesthetized dog are much less sensitive to the action of vasopressin than in the conscious dog and may in fact be unaffected by the hormone. Changes in urine flow from such kidneys have only been induced when doses of vasopressin have been given sufficient to cause vascular changes. The production of a small volume of concentrated urine under these conditions could be the result of a low renal blood flow or a low rate of filtration in the glomeruli. Any manoeuvre which caused a change in renal blood flow, an increase in glomerular filtration or increased the rate of passage of fluid in the nephron might then result in an increased urine flow resembling a small water diuresis. In the experiments reported here whenever urine flow increased the urine became more dilute and the excretion of sodium showed little change. The only exception to this was after infusion of saline when sodium excretion increased, although the concentration of sodium in the urine did not show any large changes. If the kidneys are in a state in which they are unaffected by vasopressin then it would not be expected that the diuretic response to mitral obstruction should be inhibited by infusion of vasopressin at rates of 2.5 and 10 times the antidiuretic dose. In support of this idea it may be noted that in Verney's (1929) experiments in both the anaesthetized hypophysectomized dog and with the isolated

perfused kidney maximum urine flows reached were in the region of 2 ml./min and were often much less although urea was added to the perfusate to encourage urine flow (Verney, 1926). Urine flows of this order were seen in the present experiments in dogs with an intact neurohypophysis and also began some time after a surgical procedure. Such flows sometimes occurred spontaneously especially when the anaesthetic became light and reflex movements became more frequent. In view of Theobald's (1934) observations it would be expected that such movements would lead to an increased rather than a decreased release of vasopressin.

Baisset & Montastruc (1959) claimed to haveshown that distension of the left atrium produces diuresis by inhibiting neurohypophysial release of antidiuretic hormone. They assayed an extract of jugular vein blood (Baisset, Douste-Blazy, Montastruc & Valdiguié, 1957) by injecting the extract into ethanol anaesthetized rats and comparing the effect on urine flow with that produced by injecting vasopressin. The antidiuretic activity of the extract from 0.25 ml. plasma was represented as corresponding to 0.1 m-u. vasopressin before balloon inflation and 0.06 m-u immediately after balloon inflation. The antidiuretic activity of the extract was not definitely identified as of pituitary origin and the method was said to allow assay of antidiuretic activity to within 0.02 m-u. vasopressin, the difference reported may therefore be only just within the limits of the method. If this antidiuretic activity is presumed to be of posterior pituitary

origin then as vasopressin is rapidly removed from blood (Heller, 1957; Lauson & Bocanegra, 1961), and with a carotid blood flow of 0.13 ml./kg/sec (Verney 1947) i.e. jugular venous flow about 200 ml./min in a 15 kg dog, concentrations of antidiuretic hormone of this order in the jugular venous blood indicate a continuous release of 30-40 m-u./min from the naurohypophysis. If these figures are accepted then antidiuresis in these dogs is occurring when vasopressin is added to the blood rate of 40 m-u./min but diuresis is occurring when 25 m-u./min is released. These figures are much greater than found by Verney (1954) to inhibit diuresis in the anaesthetized hypophysectomized dog (4.2 m-u./min inhibited diuresis). The only report of release of antidiuretic hormone of this order in dogs is that of Weinstein, Berne & Sachs (1960) who found a sudden excessive release of antidiuretic hormone when dogs were bled until their blood pressure fell to 50 mm Hg. When the results of Baisset & Montastruc (1959) are examined more closely several other puzzling features are seen. In Fig.2 they show an increase in urine flow occurring after a balloon was inflated in the left atrium for only five minutes. As Verney (1947) points out there is no theoretical justification for the expectation that a transient (10 min) suppression of neurohypophysial activity would evoke a significant increase in the rate of urine secretion. In Fig.3 the balloon was inflated for only three

minutes and the increase in urine flow did not occur until fifteen minutes later. The authors claimed that diuresis did not follow balloon inflation after the supra-optice hypophysial tracts had been sectioned, Fig.5 of their paper shows such an experiment; a balloon was inflated in the left atrium for three minutes and was followed by a marked fall in mean arterial pressure which lasted about twenty-five minutes; under these conditions it would indeed have been surprising if urine flow had increased.

The demonstration in the experiments of this report that the diuresis caused by obstruction of the left atrium occurred during infusion of vasopressin at ten times the rate needed to stop water diuresis in conscious animals means that the diuresis is not produced by any normal function of the neurohypophysis. If the neurohypophysis is part of the mechanism producing the diuresis, the sensitivity of the kidney to antidiuretic hormone must also be abnormal and the effect is so far removed from normal function of the neurohypophysis as to have no relevance in the study of the normal control of urine flow.

(c) PLASMA PROTEIN CONCENTRATION.

The effect on the kidney of a fall in plasma protein concentration is to cause an increased excretion of sodium and is therefore unlike any change seen on inflation of a balloon in the left atrium. In two of the present experiments there

was no change in plasma protein concentration and the diuretic response to left atrial distension cannot therefore be attributed to such a change.

(d) ARTERIAL BLOOD PRESSURE.

Marshall & Kolls (1919) compressed one renal artery in an anaesthetized dog by means of an inflatable cuff and showed that in a denervated kidney there was a reduction in sodium excretion. If the aorta is clamped in anaesthetized dogs so that renal arterial pressure falls below 70 mm Hg there is an immediate fall in urine flow and sodium excretion (Pitts & Duggan, 1950). Similarly inflating a balloon in the aorta in both anaesthetized and unanaesthetized dogs reduced urine flow when renal artery pressure fell to 80 mm Hg (Thomson, Barrett & Pitts, 1951). Chronic constriction of one renal artery (Mueller, Surtshin, Carlin & White, 1951) led to a reduction inthe excretion of salt and water from the constricted kidney; the authors consider that the changes could be adequately explained by a change in glomerular filtration too small to be detected by clearance techniques.

The effects on the kidney of an increase in blood pressure may be studied by occluding the carotid arteries (O'Connor,1955). The effects are an increased excretion of sodium chloride and bicarbonate with only a small increase in the excretion of potassium and urea, the urine becomes more alkaline and the excretion of ammonium decreases. Changes in arterial pressure

always produce an immediate effect on urine flow and the excretion of solutes. When the excretion of sodium is initially low the increase in sodium excretion is brought about by an increased sodium concentration, whereas when the initial sodium excretion is higher there is an increase in urine flow and little change or even a fall in sodium concentration. Changes in dogs undergoing water diuresis have already been discussed. In fact these changes in urinary excretion produced by a rise in arterial pressure of 40 mm Hg are comparatively small and about equal the effects of a fall of 0.1 - 0.2 g/100g in plasma solids, a change which would be produced in a dog by the ingestion of 100 ml. saline.

The concept that renal blood flow might be modified by changes in pulse pressure was initiated by Hooker (1910) as a result of his studies with the isolated perfused kidney. Gesell (1913) was unable to establish any significant effects of pulse pressure on renal blood flow in vivo, however, he was able to establish that the amount of urine eliminated varied directly with the magnitude of the pulse pressure. There were also a few experiments which suggested that sudden pressure changes and 'vascular shocks' might be an important factor in the secretion of urine. Ritter (1952) found no change in renal blood flow when pulse pressure was decreased but mean pressure maintained constant. No recent studies have been made of the effects on urine flow of changing pulse pressure. The studies

already described in which a renal artery or the aorta was clamped would cause a decrease in pulse pressure but were accompanied by a reduction in mean pressure.

Inflation of a balloon in the left atrium in anaesthetized dogs caused a fall of about 10 mm Hg in mean arterial pressure. Such a change would be expected to produce little effect on urine flow or composition but if there were any changes an immediate reduction in urine flow and sodium excretion would be expected. The diuresis could not be related in any way, either to the initial level of blood pressure or to the change when the balloon was inflated, it is therefore unlikely that the diuresis was caused by the change in mean arterial pressure produced by balloon inflation.

(a) THE RENAL NERVES.

In unanaesthetized animals or man at rest the sympathetic nerve supply to the kidney is inactive and no functional differences have been found between the fully denervated kidney and its innervated control (Smith, 1951). The observations of Merrill, Murray, Harrison & Guild (1956) and later of Bricker, Guild, Reardan & Merrill (1956) on the function of a homotransplanted kidney have fully confirmed that the renal nerves are not essential to renal function. However, section of the renal nerves in anaesthetized animals produces alterations in the volume and composition of the urine. Thus Surtshin, Mueller & White (1952) found that deep pentobarbital or ether anaesthesia

produced a fall in sodium and water excretion in a normal kidney but not a denervated one. Berne (1952) confirmed these observations and found in dogs anaesthetized with pentobarbitone or chloralose that the innervated kidney had a lower para-amino-hippuric acid clearance, lower creatinine clearance and a lower rate of sodium excretion than the denervated kidney. Similar but larger changes may be produced by stimulation of the renal nerves (Houck, 1951). The effect of activity in the renal nerves is thus similar to the effects of a fall in arterial pressure and Marshall & Kolls (1919) showed that the changes produced by compression of the renal artery could be reversed by cutting the splanchnic nerves. Surtshin & Hoeltzenbein (1954) concluded that any effects of splanchnic nerve section were solely due to minor changes in glomerular filtration often undetected by clearance measurements. Although the denervated kidney functions normally in conscious subjects this does not exclude the possibility that during circulatory stress such as exercise or during postural changes profound alterations in renal function may not be mediated through the haemodynamic effects of renal nerves (Pappenheimer, 1960).

When a balloon was inflated in the left atrium similar changes in urine flow and composition occurred in the denervated and innervated kidney and the diuretic response to balloon inflation was therefore not dependant upon any change in the activity of the renal nerves.

(f) ADRENALINE AND NORADRENALINE.

The usual effect of an infusion of adrenaline or noradrenaline into human subjects is to cause a fall in the excretion of sodium and potassium (Smythe, Nickel & Bradley, 1952). The effects of infusion into animals have been reviewed by Pickford (1952). When adrenaline is infused into conscious dogs at a rate of 0.1 - 0.2 μg/kg/min there is an immediate decrease in sodium excretion and sometimes urine flow even during water diuresis (O'Connor, 1958b). To produce similar urinary changes a larger dose of noradrenaline had to be used, 0.2 - 0.4 μg/kg/min and this caused an increase in arterial pressure and a slowing of the heart rate (O'Connor, 1958 b). Noradrenaline in equivalent doses is always less strongly antidiuretic than adrenaline and in the presence of atropine may even cause a sharp temporary rise in urine flow (Pickford & Watt, 1951). In anaesthetized animals noradrenaline may cause a diuresis and an increase in sodium excretion when given in doses sufficient to raise the blood pressure (Handley & Moyer, 1954). When arterial pressure is held constant however the smallest amount of noradrenaline may cause a fall in urine flow (Langston & Guyton, 1958). It seems likely therefore that if noradrenaline produces a diuresis then this is secondary to a rise in arterial pressure, which may overcome the renal effect of the drug which is to cause vasoconstriction.

In the present series of experiments infusion of noradrenaline at rates between 0.1 - 0.8 μg/kg/min was sometimes accompanied by an increase in urine flow but never by a decrease although

sodium excretion sometimes fell. When there was an increase in urine flow during an infusion of noradrenaline urine sodium concentration fell so that sodium excretion was relatively unchanged. Infusion of noradrenaline at this rate caused a slowing of the heart rate and an increased pulse pressure (Fig.10) and it is likely that the urinary changes were the result of an altered renal blood flow.

(g) THE PLASMA CONCENTRATION OF SOLUTES.

If the plasma concentration of an individual substance is raised then there is an individual and a general effect on urinary excretion (O'Connor, 1962). The individual effect is to increase the urinary excretion of the substance; the general effect is produced if there is a large increase in the urinary excretion of solutes, the urinary volume then increases(osmotic diuresis) and if the diuresis is large enough there will also be increased excretion of sodium and chloride.

Inflation of a balloon in the left atrium caused an increase in urine flow during which the urine always became more dilute and there were therefore only small increases in the excretion of urinary solutes. This applied to individual solutes measured, sodium, potassium, ammonium and glucose and also to the total urine solutes. If the diuresis were an osmotic diuresis the excretion of osmotically active solutes should increase nearly in proportion to the urine volume. If a large amount of an organic anion entered the plasma and was excreted in the urine during balloon inflation then the urine would

become more acid and contain ammonium. In these experiments the urine pH was usually about 7.0 and showed only small inconsistent changes.

(h) HORMONES OF THE ADRENAL CORTEX.

It has been suggested by several workers that the excretion of sodium and potassium and thereby the electrolyte content of the body may be controlled by variations in the secretion of aldosterone from the adrenal cortex. This theory often implies that the secretion of aldosterone may be inhibited by expansion of the 'low pressure' part of the vascular system (Summarized by Bartter & Gann, 1960). In particular Farrell (1958) has claimed that traction on the right atrium in anaesthetized animals reduces aldosterone secretion. This theory has recently been criticised by O'Connor (1962) and by Davis (1961) and will not be further discussed here.

The diuresis induced by inflation of a balloon in the left atrium is unlike any effect to be expected from a reduction in the secretion of adrenal cortical hormones. If adrenal steroids are injected into adrenalectomized animals the effects appear in about two hours and last 8-12 hours after the injection (O'Connor, 1962). When injected into normal animals or human subjects no immediate changes in the urinary excretion of electrolytes can be detected (Gowenlock, Mills & Thomas, 1959). It is therefore most unlikely that any effect of reduced secretion of aldosterone would produce changes in urine flow

or composition within fifteen minutes of inflation of a balloon in the left atrium.

4. CONCLUSIONS CONCERNING THE DIURETIC RESPONSE TO LEFT ATRIAL DISTENSION.

The agent acting on the kidney to produce diuresis during left atrial distension cannot be identified. However, renal function in these anaesthetized dogs does appear to differ in several respects from that in the normal dog. Firstly, renal blood flow is probably low and although increased by denervation of the kidney may still be less than in the normal dog. Secondly, it has not been possible to show that vasopressin exerts its usual effects on the kidney in the anaesthetized dog; only when doses are given large enough to cause vasoconstriction is there any effect on urine flow. Thirdly, a number of manoeuvres likely to cause changes in renal blood flow, infusion of blood or plasma, infusion of noradrenaline, increasing the heart rate and a lightening of the anaesthetic cause a transient dilute diuresis.

Attempts to define the afferent mechanisms leading to diuresis have been unsuccessful. Obstructing the mitral orifice and inflating balloons in the pulmonary veins causes diuresis but also cardiovascular changes. Blocking or destroying nervous pathways in the thorax prevents the diuresis but also changes the cardiovascular response. The diversity of the manoeuvres causing diuresis suggests the possibility that the diuresis is the result of a non-specific effect on the kidney and that the characteristic urinary changes depend on the kidney

itself. Thus a change in renal blood flow or even an alteration in the pulsations the kidney is subjected to, might cause a more rapid flow of fluid through the nephron and in a kidney insensitive to antidiuretic hormone produce a diuresis of dilute urine.

The diuretic response to inflation of a balloon in the left atrium does resemble the diuresis of negative pressure breathing. They have a similar time course, are of comparable size and during both sodium excretion remains constant. The mechanisms involved in producing the diuresis cannot at present be satisfactorily explained.

B. LEFT ATRIAL DISTENSION AND HEART RATE.

It was shown that when the circulation was obstructed by inflating a balloon in the left atrium there was an increase in heart rate and although at the same time mean arterial blood pressure and pulse pressure decreased these changes were not consistently related to one another. When small balloons were inflated in the left pulmonary veins there was invariably an immediate increase in heart rate which was maintained, with small variations, as long as the balloons were kept distended and then decreased within a few minutes when the balloons were deflated. It was believed that this procedure did not obstruct the flow of blood through the left atrium and there was usually a small increase in mean arterial pressure, although pulse pressure decreased.

In spite of many attempts to confirm Bainbridge's (1915) theory that stimulation of receptors in the atria caused a reflex increase in heart rate, there has been no satisfactory demonstration of any reflex cardiovascular effects caused by stimulation of atrial receptors. It is outside the scope of this work to discuss in detail the experiments that have been made, and these have been fully reviewed by Aviado & Schmidt (1955) and Heymans & Neil (1958). The conclusion most usually reached by investigators is that distension of the atria causes bradycardia and hypotension, this finding has also been accepted by some reviewers (Neil, 1960). It is believed that the experiments described in this work provide the first demonstration that an increase in heart rate may be produced regularly by stretching only that part of the left atrial wall in which the majority of the sensory nerve endings lie. The mechanism by which the increase in heart rate occurs has not yet been investigated.

CHAPTER II

CONCLUSIONS CONCERNING THE THEORY OF VOLUME RECEPTORS.

In Part I, Chapter III, it was pointed out that most of the urinary effects of manoeuvres which change intrathoracic blood volume could be explained by changes in glomerular filtration. The theory that the volume of the body fluid is controlled by the stimulation of stretch receptors in the intrathoracic circulation is based on the appearance of a transient diuresis during negative pressure breathing, obstruction of the mitral orifice, saline infusions and lying down. The diuresis is small averaging only one eighth of maximal water diuresis in dogs and one third of maximal water diuresis in human subjects (Smith, 1957). It has not been possible to define conditions to ensure the regular appearance of the diuresis but it has been described most frequently in chloralose anaesthetized dogs and in hydrated human subjects at rest. Diminished release of antidiuretic hormone would explain some of the features of the diuresis but it occurs in anaesthetized dogs during infusion of vasopressin, although in conscious human subjects vasopressin prevents the appearance of the diuresis. Two conditions seem to be necessary for the production of the diuresis; a procedure causing a significant cardiovascular change, and the kidney only minimally under the influence of antidiuretic hormone.

The experiments described in this thesis show that distension of the left atrium does not cause diuresis by causing a diminished

release of antidiuretic hormone from the neurohypophysis. The mechanisms involved in the production of this diuresis cannot at present be explained in terms of agents known to act on the kidneys, nor can the diuretic response to negative pressure breathing and lying down be explained. Until these small diureses can be adequately explained they do not provide sufficient evidence on which to base a theory that intrathoracic receptors exert a control upon urine flow. The results of experiments on negative pressure breathing and left atrial distension should not therefore be used to explain other circumstances in which urine flow changes. Similarly attempts to explain pathological variations in body fluid volume (Pearce 1961; Gauer, Henry & Sieker, 1961) in terms of altered function of cardiac receptors must be condemned. Unfortunately the theory that atrial receptors influence neurohypophysial secretion has already been incorporated in some text books (Ruch & Fulton, 1960; Keele & Neil, 1961) and it will be difficult to discourage further attempts to correlate observed pathological changes in body fluid volume with this theory.

A C K N O W L E D G E M E N T S.

Foremost I must thank Professor A. Hemingway for the encouragement, advice and helpful criticism he has given me throughout the whole period of this work.

I wish to thank especially Dr. W.J. O'Connor and Dr. R.J. Linden who participated in the experiments and whose invaluable advice, given freely during our many discussions, provided the stimulus which enabled me to complete this work.

I should also like to thank my mother, Mrs. C. Ledsome, who has typed the manuscript carefully and skillfully and thereby greatly reduced my task.

I am grateful to Mr. J. Brook for the willing and expert assistance he gave me during the experiments, and to Mr. P.W. Hargreaves who spent many hours preparing the photographic reproductions.

Lastly I should like to thank my wife without whose cooperation and patient understanding I could not have written this thesis.

PART IV.

BIBLIOGRAPHY.

Adrian, E.D. (1926). The impulses produced by sensory nerve endings. J.Physiol. 61, 49 - 72.

Adrian, E.D. (1933). Afferent impulses in the vagus and their effect on respiration. J.Physiol. 79, 332 - 358.

Agostini, E., Chinnock, J.E., Daly, M de B. & Murray, J.G.(1957). Functional and histological studies of the vagus nerve and its branches to the heart, lungs and abdominal viscera of the cat. J.Physiol. 135, 182 - 205.

Allen, T.H., Walzer, R.A., Gregersen, K. & Gregersen, M.I. (1959). Blood, volume, bleeding volume and tolerance to haemorrhage in the splenectomized dog. Amer.J.Physiol. 196, 176 - 178.

Allison, J.B., Cole, W.H., Holmes, J.H. & Root, W.S. (1947). The effect of haemorrhage and muscle trauma upon the blood phosphate of dogs. Amer.J.Physiol. 149, 424 - 428.

Altschule, M.D. & Gilligan, D.R. (1938). The effects of the cardiovascular system of fluids administered intravenously in man. II. The dynamics of the circulation. J.clin. Invest. 17, 401 - 411.

Amann, A. & Schaefer, H. (1943). Uber sensible Impulse im Herznerven. Pflug.Arch.ges.Physiol. 246, 757 - 789.

Armin, J. & Grant, R.T. (1955). Vasoconstrictor activity in the rabbits blood and plasma. J.Physiol. 128, 511 - 540.

Asmussen, E., Christensen, E.H. & Neilsen, M. (1940). Regulation of circulation in different postures. Surgery, 8. 604-616.

Atkins, E.L. & Pearce, J.W. (1959). Mechanisms of the renal response to plasma volume expansion. Can.J.Biochem. Physiol. 37, 91 - 102.

Aviado, D.M. & Schmidt, C.F. (1955). Reflexes from stretch receptors in blood vessels, heart and lungs. Physiol. Rev. 35, 247 - 300.

Bainbridge, F.A. (1915). The influenceof venous filling upon the rate of the heart. J. Physiol. 50, 65 - 84.

Baisset, A., Douste-Blazy, L., Montastruc, P. & Valdeguie, P.(1957) Reduction du pouvoir antidiuretique du sang apres distension auriculaire chez le chien. C.R.Soc.Biol. Paris, 151, 378 - 382.

Baisset, A. & Montastruc, P. (1959). Modifications de la diurese apres distension de l'oreillette gauche, role de l'hormone antidiuretique. Pathol. Biologie. 7, 1691 - 1702.

Barach, A.L., Eckman, M., Ginsburg, E., Rumsey, C.C., Korr, I., Eckman, I. & Besson, G. (1946). Studies on positive pressure respiration. I. General aspects and types of pressure breathing. II. Effects on respiration and circulation at sea level. J.Aviat.Med. 17, 290 - 320.

Baratz, A. & Ingraham, C. (1960). Renal haemodynamics and antidiuretic hormone release associated with volume regulation. Amer.J.Physiol, 198, 565 - 570.

Barbour, A., Bull, G.M., Evans, B.M., Hughes Jones, N.C. & Logothetopoulos, J. (1953). The effect of breathing 5% to 7% carbon dioxide on urine flow and mineral excretion. Clin.Sci. 12, 1 - 13.

Bartter, F.C. & Gann, D.S. (1960). On the hemodynamic regulation of the secretion of aldosterone. Circulation 21, 1016 - 1023.

Bayliss, L.E., (1959). 'Principles of General Physiology'. Vol.I. 5th Ed. London: Longmans Green & Co.Ltd. p.101.

Bayliss, L.E. & Fee, A.R. (1930). Studies on water diuresis. III. A comparison of the excretion of urine by innervated and denervated kidneys perfused with the heart-lung preparation. J.Physiol. 69, 135 - 143.

Beecher, H.K., Bennett, H.S. & Bassett, D.L. (1943). Circulatory effects of increased pressure in the airway. Anaesthesiology. 4, 612 -618.

Berkley, H.J. (1894). The intrinsic nerve supply of the cardiac ventricles in certain vertebrates. Johns Hopkins Hosp. Rep. 4, 248 - 255.

Berliner, R.W. & Davidson, D.G. (1957). Production of hypertonic urine in the absence of pituitary antidiuretic hormone. J.clin.Invest. 36, 1416 - 1427.

Bernard, C. (1878). Lecons sur les phenomenes de la vie communs aux animaux et aux vegetaux. Paris: J.B. Balliere et Fils, 1, 111 - 114.

Berne, R.M. (1952). Haemodynamics and sodium excretion of denervated kidney in anaesthetized and unanaesthetized dogs. Amer.J.Physiol. 171, 148 - 158.

Bevegard, S., Holmgren, A. & Johnson, B. (1960). The effect of body position on the circulation at rest and during exercise, with special reference to the influence on the stroke volume. Acta. physiol.scand. 49, 279 - 298.

Bianconi, R. & Green, J.H. (1959a). Cardio respiratory afferent fibres in the vagus of the cat. Arch.Sci.Biol. 43, 454-463.

Bianconi, R. & Green, J.H. (1959b). Pulmonary baroreceptors in the cat. Arch.ital.Biol. 97, 305 - 315.

Bjurstedt. H. (1953). Influence of the abdominal muscle tone on the circulatory response to positive pressure breathing in anaesthetized dogs. Acta.physiol.scand. 29, 145-162.

Bliss, J.Q., Johns,D.C. & Burgen, A.S.V. (1959). Transfusion reactions due to plasma incompatability in dogs. Circulation. Res. 7, 79 - 85.

de Bodo, R.C. & Bloch, H.I. (1941). The effect of narcotics on diuresis. J.Pharmacol. 72, 4.

Bojesen, E. (1954). The renal mechanism of "Dilution Diuresis" and salt excretion in dogs. Acta.physiol.scand. 32, 129 - 147.

Borst, J.G.G. (1948). The maintenance of an adequate cardiac output by the regulation of the urinary excretion of water and sodium chloride; an essential factor in the genesis of oedema. Acta.med.scand. 130 (suppl.207),1 - 71.

Boyd, J.D. (1941). The nerve supply of the mammalian ductus arteriosus. J.Anat. Lond. 75, 457 - 468.

Boylan, J.W. & Antkowiak, D.E. (1959). Mechanism of diuresis during negative pressure breathing. J.appl.Physiol. 14, 116 - 120.

Brannon, E.S., Stead, E.A., Warren, J.V. & Merrill, A.J. (1946). Haemodynamics of acute haemorrhage in man. Amer.Heart J. 31. 407 - 412.

Brecher, G.A. (1956). Venous return. New York: Grune & Stratton.

Bricker, N.S., Guild, W.R., Reardan, J.B. & Merrill, J.P. (1956). Studies on the functional capacity of a denervated homotransplanted kidney. J.clin.Invest. 35, 1364-1380.

Brigden, W., Howarth, S. & Sharpey-Schafer, E.P. (1950). Postural changes in the peripheral blood flow of normal subjects with observations on vasovagal fainting reactions as a result of tilting, lordotic posture, pregnancy and spinal anaesthesia. Clin.Sci. 9, 79 - 90.

Bronk, D.W. (1931). Afferent impulses in the carotid sinus and aortic nerves. Pro.Soc.exp.Biol. N.Y. 28, 1014.

Brun, C., Knudsen, E.O.E. & Raaschou, F. (1945a). The influence of posture on the kidney function. I. Acta.med.scand. 122, 315 - 331.

Brun, C., Knudsen, E.O.E. & Raaschou, F. (1945b). The influence of posture on the kidney function. II. Acta, med.scand. 122, 332 - 341.

Brun, C., Knudsen, E.O.E. & Raaschou, F. (1945c). Post-syncopal oliguria. Kidney function and circulatory collapse. Acta.med.scand. 122. 381 - 395.

Brun, C., Knudsen, E.O.E. & Raaschou, F. (1945d). On the cause of post-syncopal oliguria. Acta.med.scand. 122, 486 - 500.

Bulbring, E., Burn, J.H. & Walker, J.M. (1949). Reduction in coronary flow by pituitary (posterior lobe) extract in relation to the action of nicotine and to smoking. Quart.J.Med. 18, 73 - 80.

Bulbring, E. & Whitteridge, D. (1945). The activity of vagal stretch endings during congestion in perfused lungs. J.Physiol. 103, 477 - 487.

Cahoon, D.H., Michael, I.E. & Johnson, V. (1941). Respiratory modification of the cardiac output. Amer.J.Physiol, 133, 642 - 650.

Cannon, W.B. (1932). 'The wisdom of the body'. London: Kegan, Paul, Trench, Trubner & Co.Ltd. p.270.

Carr, D.T. & Essex, H.E. (1946). Certain effects of positive pressure respiration on the circulatory and respiratory systems. Amer. Heart J. 31, 53 - 73.

Chapman, K.M. & Pearce, J.W. (1959). Vagal afferents in the monkey. Nature. 184, 1237 - 1238.

Cole, W.H., Allison, J.B., Murray, T.J., Boyden, A.A., Anderson, J.A. & Leathem, J.H. (1944). Composition of the blood of rabbits in gravity shock. Amer.J.Physiol. 141, 165 - 171.

Coleridge, J.C.G., Hemingway, A., Holmes, R.L.,& Linden, R.J.(1957). The location of atrial receptors in the dog: A physiological and histological study. J.Physiol. 136, 174 - 197.

Coleridge, J.C.G. & Kidd, C. (1960). Electrophysiological evidence of baroreceptors in the pulmonary artery of the dog. J.Physiol. 150, 319 - 331.

Coleridge, J.C.G. & Kidd, C. (1961). Relationship between pulmonary arterial pressure and impulse activity in pulmonary arterial baroreceptor fibres. J.Physiol. 158, 197 - 205.

Coleridge, J.C.G., Kidd, C. & Sharp, J.A. (1961). The distribution, connections and histology of baroereceptors in the pulmonary artery, with some observations on the sensory innervation of the ductus arteriosus. J.Physiol. 156, 591 - 602.

Coleridge, J.C.G. & Linden, R.J. (1955). The effect of intravenous infusions upon the heart rate of the anaesthetized dog. J.Physiol. 128, 310 - 319.

Coleridge, J.C.G. & Linden, R.J. (1959). The variations with respiration in effective right and left atrial pressures. in the dog. J.Physiol. 145, 482 - 493.

Conway, E.J. (1957). 'Microdiffusion analysis and volumetric Error'. 4th Ed., p.90. London: Crosby Lockwood & Sons Ltd.

Costantin, Le Roy L. (1959). Effect of pulmonary congestion on vagal afferent activity. Amer.J.Physiol. 196, 49 - 53.

Crawford, B. & Ludemann, H. (1951). The renal response to intravenous injection of sodium chloride solutions in man. J. clin. Invest. 30, 1456 - 1462.

Currie, J.C.M. & Ullmann, E. (1961). Polyuria during experimental modifications of breathing. J.Physiol. 155, 438 - 455.

Daly, M.de Burgh & Evans, D.H.L. (1953). Functional and histological changes in the vagus nerve of the cat after degenerative section at various levels. J.Physiol, 120, 579 - 595.

Davies, D.F. & Shock, N.W. (1950). The variability of measurement of inulin and diodrast tests of kidney function. J.clin.Invest. 29, 491 - 495.

Davis, J.O. (1961). A critical evaluation of the role of receptors in the control of aldosterone secretion and sodium excretion. Progr.cardiovasc.Dis. 4, 27 - 46.

Dawes, G.S. (1953). Reflex factors in the regulation of the circulation. In 'Shock and circulatory Homeostasis'. Ed. H.D. Green, New York, Josiah Macy, Jr. Foundation.

Dawes, G.S. & Widdicombe, J.G. (1953). The afferent pathway of the Bezold reflex: the left vagal branches in dogs. Brit.J.Pharmacol. 8, 395 - 398.

De Graff, A.C. & Sands, J. (1925). Are reflexes from the large veins or auricle of importance in the regulation of the circulation ? Amer.J.Physiol. 74, 400 - 415.

Dicker, S.E. (1956). Standard renal clearance in mammals. In

'Modern views on the secretion of urine', Ed.F.R,Winton, London: Churchill.

Dickinson, C.J. (1950). Afferent nerves from the heart region. J.Physiol. 111, 399 - 407.

Dole, V.P., Emerson, K.jr., Phillips, R.A., Hamilton, P. & Van Slyke, D.D. (1946). The renal extraction of oxygen in experimental shock. Amer.J.Physiol. 145, 337 - 345.

Dow, P. (1939). The venous return as a factor affecting vital capacity. Amer.J.Physiol. 127, 793 - 795.

Doyle, J.T., Wilson, J.S., Estes, E.H. & Warren, J.V. (1951). The effect of intravenous infusions of physiologic saline solution on the pulmonary arterial and pulmonary capillary pressure in man. J.clin.Invest. 30, 345 - 352.

Drury, D.R., Henry, J.P. & Goodman, J. (1947). The effects of continuous pressure breathing on kidney function. J.clin.Invest. 26, 945 - 951.

Duke, H.N., Pickford, M.& Watt, J.A. (1951). The antidiuretic action of morphine: its site and mode of action in the hypothalamus of the dog. Quart.J.exp.Physiol. 36, 149 - 158.

van Dyke, H.B. & Ames, R.G. (1951). Alcohol diuresis. Acta. Endocr., Copenhagen. 7, 110 - 121.

van Dyke, H.B., Engel, S.L. & Adamsons, K.jr. (1956). Comparison of pharmacological effects of lysine and arginine vaso - pressins. Proc.Soc.exp.Biol. N.Y. 91, 484 - 486.

Ead, H.W., Green, J.H. & Neil, E. (1952). A comparison of the effects of pulsatile and non-pulsatile blood flow through

the carotid sinus on the reflexogenic activity of the sinus baroreceptors in the cat. J.Physiol. 118, 509-519.

Ebert, R.V., Stead, E.A. & Gibson, J.G. (1941). Response of normal subjects to acute blood loss. Arch.intern.Med. 68, 578 - 590.

Edholm, O.G. (1940). Effect of gravity on the blood pressure of the cat. J.Physiol. 98, 79 - 96.

Einthoven, W. (1908). On vagus currents examined with the string galvanometer. Quart.J.exp.Phys. 1, 243 - 246.

Einthoven, W. (1911). Verh.des.Ges. d. Naturf. p.93. Cited by Adrian, E.D. in J.Physiol, 1926, 61, 49 - 72.

Eisen, V.D. & Lewis A.A.G. (1954). Antidiuretic activity of human urine after surgical operations. Lancet 267, 361 - 362.

Elftman, A.G. (1943). Theafferent and parasympathetic innervation of the lungs and trachea of the dog. Amer.J.Anat. 72, 1 - 27.

Epstein, F.H. & Goodyear, A.V.N., Lawrason, F.D. & Relman, A.S. (1951). Studies of the antidiuresis of quiet standing: the importance of changes in plasma volume and glomerular filtration rate. J.clin.Invest. 30, 63 - 72.

von Euler, U.S. (1951). The nature of adrenergic nerve mediators. Pharmacol. Rev. 3, 247 - 277.

von Euler, U.S., Luft, R. & Sundin, T. (1955). The urinary excretion of noradrenaline and adrenaline in healthy subjects during recumbency and standing. Acta.physiol.scand. 34, 169 - 174.

Eyster, J.A.E. & Middleton, W.S. (1924). Cardio-vascular reactions to haemorrhage and transfusion in man. Amer.J.Physiol. 68, 581 - 584.

Farrell, G. (1959). The physiological factors which influence the secretion of aldosterone. Recent Progr. Hormone Res. 15, 275 - 310.

Fenn, W.O. & Chadwick, L.E. (1947). Effect of pressure breathing on blood flow through the finger. Amer. J.Physiol, 151, 270 - 275.

Fenn, W.O., Otis, A.B., Rahn, H., Chadwick, L.E. & Hegnauer, A.H. (1947). Displacement of blood from the lungs by pressure breathing. Amer.J.Physiol, 151, 258 - 269.

Ferguson, T.B., Shadle, O.W. & Gregg D.E.(1953). Effect of blood and saline infusion on ventricular end diastolic pressure, stroke work, stroke volume and cardiac output in the open and closed chest dog. Circulation Res. 1. 62 - 68.

Fine, J. (1935). Benedict's qualitative test. Brit.Med.J.2, 1169 - 1170.

Fitzhugh, F.W.jr., McWhorter, R.L.Jr., Estes, E.H.jr., Warren, J.V. & Merrill, A.J. (1953). The effect of application of tourniquets to the legs on cardiac output and renal function in normal human subjects. J.clin.Invest, 32, 1163 - 1170.

Floyd, W.F., & Neil, E. (1952). The influence of the sympathetic innervation of the carotid bifurcation on chemoceptor and baroceptor activity in the cat. Arch.int.Pharmacodyn, 91, 230 - 239.

Folin, O & Wu, H. (1919). A system of blood analysis. J. biol. Chem. 38, 81 - 110.

Gauer, O.H., Henry, J.P., Sieker, H.O. (1956). Changes in central venous pressure after moderate haemorrhage and transfusion in man. Circulation Res. 4, 79 - 84.

Gauer, O.H., Henry, J.P. & Sieker, H.O. (1961). Cardiac receptors and fluid volume control. Progr.Cardiovasc.Dis. 4, 1 - 26.

Gauer, O.H., Henry, J.P., Sieker, H.O. & Wendt, W.E. (1954). The effect of negative pressure breathing on urine flow. J. clin. Invest 33, 287 - 296.

Gauer, O.H., Sieker, H.O. (1956). The continuous recording of central venous pressure changes from an arm vein. Circulation Res. 4, 74 - 78.

Gerst, P.H., Rattenborg, C. & Holaday, D.A. (1959). Effects of haemorrhage on pulmonary circulation and respiratory gas exchange. J. clin. Invest. 38, 524 - 538.

Gesell, R.A. (1913). On the relation of pulse pressure to renal secretion. Amer.J.Physiol. 32, 70 - 93.

Ginsburg, M. & Brown, L.M. (1957). The effects of haemorrhage and plasma hypertonicity on the neurohypophysis; in 'The neurohypophysis' Ed. H.Heller. London: Butterworths, 109 - 123.

Goodyear, A.V.N., Peterson, E.R. & Relman, A.S. (1949). Some effects of albumin infusions on renal function and electrolyte excretion in normal man. J.appl.Physiol. 1, 671 - 682.

Gowenlock, A.H., Mills, J.N. & Thomas, S. (1959). Acute postural changes in aldosterone and electrolyte excretion in man. J.Physiol. 146, 133 - 141.

Grant, R.T. & Reeve, E.B. (1951). Observations on the general effects of injury in man with special reference to wound shock. Special Rept.No.277, Medical Research Council. London: H.M.Stationery Office.

del Greco, F. & de Wardener, H.E. (1956). Effects on urine osmolarity of a transient reduction in glomerular filtration rate and solute output during a'water' diuresis. J. Physiol. 131, 307 - 316.

Grossman, J. (1957). Volume factors in body fluid regulation. Arch. intern. Med. 99, 93 - 128.

Guyton, A.C., Lindley, J.E., Touchstone, R.N., Smith, C.M. & Batson, H.M.Jr. (1950). Effects of massive transfusion and haemorrhage on blood pressure and fluid shifts. Amer.J.Physiol. 163, 529 - 538.

Hamilton, W.F. & Morgan, A.B. (1932). Mechanism of the postural reduction in vital capacity in relation to orthopnea and storage of blood in the lungs. Amer.J.Physiol. 99, 526 - 533.

Handley, C.A.,& Moyer, J.H. (1954). Changes in sodium and water excretion produced by vasoactive and by ganglionic and adrenergic blocking agents. Amer.J.Physiol. 178, 309 - 314.

Harrison, C.R. & Wilson, J.R. (1950). Cardiovascular, renal and general effects of large rapid plasma infusions in convalescent men. J. clin. Invest. 29, 251 - 257.

Heller, H. (1957). The metabolism and fate of the neurophypophysial principles. in 'The Neurophypophysis', London: Butterworths, 77 - 94.

Henderson, L.J. (1916). On volume in biology. Proc.nat.Acad. Sci., Wash. 2, 654 - 658.

Henderson, Y. & Haggard, H.W. (1922). Haemorrhage as a form of asphyxia. J.Amer.med.Ass. 78, 697-704.

Henry, J.P. (1955). Orthostasis and the kidney. W.A.D.C. Technical Report. 55 - 478.

Henry, J.P., Gauer, O.H. & Reeves, J.L. (1956). Evidence of the atrial location of receptors influencing urine flow. Circulation Res. 4, 85 - 90.

Henry, J.P., Gauer, O.H. & Sieker, H.O. (1956). The effect of moderate changes in blood volume on left and right atrial pressures. Circulation Res. 4, 91 - 94.

Henry, J.P., Gauer, O.H. & Sieker, H.O., Wendt, W.E., Reeves, J.L. & Lee, M.F. (1953). Effects of obstruction of pulmonary vascular bed and interference with thoracic vago sympathetics on urine flow. Abstr. XIX int.physiol. Congr, 453 - 454.

Henry, J.P., Jacobs, H., Meehan, H. & Karstens, A. (1948). The effect of pressure breathing on circulating blood volume. Fed. Proc. 7, 53.

Henry, J.P. & Pearce, J.W. (1956). The possible role of cardiac atrial stretch receptors in the induction of changes in urine flow. J.Physiol. 131, 572 - 585.

Heymans, C. & Neil, E. (1958). 'Reflexagenic areas of the cardiovascular system'. London: Churchill.

Hickler, R.B., Well, R.E.Jr., Tyler, H.R. & Hamlin, J.T. (1959). Plasma catecholamine and electroencephalographic response toacute postural change. Amer.J.Med. 26, 410-423.

Hill, L., Barnard, H. & Sequeira, J.H. (1897). The effect of venous pressure on the pulse. J.Physiol. 21, 147 - 159.

Hill, L. & Barnard,H. (1897). The influence of the force of gravity on the circulation, part II. J. Physiol. 21, 323 - 352.

Holgate, J.A. & O'Connor, W.J. (1958). The effects of infusion of adrenaline and noradrenaline onthe heart rate and arterial blood pressure of conscious dogs. Quart.J.exp. Physiol. 43, 361 - 367.

Holmes, R. & Torrance, R.W. (1959). Afferent fibres of the stellate ganglion. Quart.J.exp.Physiol. 44, 271 - 281.

Holt, J.P. (1941). The collapse factor in the measurement of venous pressure. Amer.J.Physiol. 134, 292 - 299.

Holt, J.P. (1943). The effect of positive and negative intrathoracic pressure on peripheral venous pressure in man. Amer.J.Physiol. 139, 208 - 211.

Holt, J.P. (1944). Theeffect of positive and negative intra-thoracic pressure on cardiac output and venous pressure in the dog. Amer.J.Physiol. 142, 594 - 603.

Hooker, D.R. (1910-1911). A study of the isolated kidney, the the influence of pulse pressure upon renal function. Amer.J.Physiol. 27, 24 - 44.

Houck, C.R. (1951). Alterations in renal haemodynamics and function in separate kidneys during stimulation of the renal artery nerves in dogs. Amer.J.Physiol. 167- 523-530.

Huggett, A.St.G. (1924). Studies on the respiration and circulation of the cat. IV. The heart output during respiratory obstruction. J. Physiol. 59, 373 - 380.

Huggins, R.A., Deavers, S. & Smith, E.L. (1958). Changes in circulating plasma and proteins following graded transfusions in the dog. Amer.J.Physiol. 193, 581-583.

Hulet, W.H. & Smith, H.W. (1959). Negative pressure respiration water diuresis and natriuresis in normotensive hypertensive and prehydrated normotensive subjects. J. clin. Invest. 38, 1972 - 1980.

Hulet, W.H. & Smith, H.W. (1961). Postural natriuresis and urine osmotic concentration in hydropenic subjects. Amer. J. Med. 30, 8 - 25.

Humphreys, G.H., Moore, R.L., Maier, H.C. & Apgar, V. (1938). Studies of the cardiac output of anaesthetized dogs during continuous and intermittent inflation of the lungs. J. Thoracic Surg. 7, 438 - 451.

Jahn, H., Stephan, F. & Stahl, J. (1960). Activite diuretique dans le sang et les urines apres saignee chez le chien. Arch. Sci. physiol. 14, 421 - 433.

Jarisch, A. & Zotterman, Y. (1948). Depressor reflexes from the heart. Acta. physiol. scand. 16, 31 - 51.

Jones, J.V. (1953). The afferent pathway of the Bezold reflex: the right vagal branches in cats. Brit.J.Pharmacol. 8, 352 - 355.

Keele, C.A. & Neil, E. (1961). 'Samson Wright's Applied Physiology'. London: Oxford Univ.Press.

Kilburn, K.H. & Sieker, H.O. (1960. Haemodynamic effects of continuous positive and negative pressure breathing in normal man. Circulation Res. 8, 660 - 669.

King, A.B. (1939). Nerve endings in the cardiac muscle of the rat. Johns Hopkins Hosp. Bull. 65, 489 - 499.

Klisiecki, A., Pickford, M., Rothschild, P. & Verney, E.B. (1933). The absorbtion and excretion of water by the mammal. Part I. The relationship between absorbtion of water and its excretion by the innervated and denervated kidney. Part II. Factors influencing the response of the kidney to water ingestion. Proc.Roy.Soc.B. 112, 496 - 520, 521 - 547.

Knoefel, P.K., Handley, C.A. & Huggins, R.A. (1953). Renal functions during positive pressure respiration. Proc.Soc.Exper.Biol. N.Y. 82, 430 - 432.

Knowlton, F.P. (1911). The influence of colloids on diuresis. J. Physiol. 43, 219 - 231.

Knowlton, G.C. & Larrabee, M.G. (1946). A unitary analysis of pulmonary volume receptors. Amer.J.Physiol. 147, 100-114.

Kochmann, M. (1923. Schlafmittel. Handbuch der experimentellen Pharmakologie, Ed. Hefter, A. 1, 1389 - 1448. Berlin: Springer.

Kondo, B. & Katz, L.N. (1945). Heart size in shock produced by venous occlusion of the hind limbs of the dog. Amer.J.Physiol. 143, 77 - 82.

Koster, G. & Tschermak, A. (1903). Ueber den Nervus depressor als Reflexnerv der Aorta. Pflug.Arch.Ges. Physiol. 93, 24 - 38.

Ladd, M. (1951a). Effect of prehydration on the response to saline infusion in man. J.appl.Physiol. 3, 379 - 387.

Ladd, M. (1951b). Effect of prehydration upon renal excretion of sodium in man. J.appl.Physiol. 3, 603 - 609.

Landis, E.M., Jonas, L., Angevine, M. & Erb, W. (1932). The passage of fluid and protein through the human capillary wall during venous congestion. J.clin.Invest. 11, 717-734

Landis, E.M., Brown, E., Fateux, M. & Wise,C. (1946). Central venous pressure in relation to cardiac "competence", blood volume and exercise. J.clin.Invest. 25, 237-255.

Landgren, S., Neil, E.,& Zotterman, Y. (1952). Response of carotid baroceptors to local administration of drugs. Acta. physiol. scand. 25, 24 - 37.

Langrehr, D. (1960a). Entladungsmuster und allgemeine Reizbedingungen von Vorhofsreceptoren bei Hund und Katze. Pflug. Arch. ges. Physiol. 271, 257 - 269.

Langrehr, D. (1960b). Beziehungen zwischen Vorhofsreceptor-aktivitaten und Herzmechanik von Hund und Katze bei verschiedenen Kreislaufzustanden. Pflug.Arch. ges. Physiol. 271, 270 - 282.

Langrehr, D. & Kramer, K. (1960). Beziehungen der mittleren Impulsfrequenz von Vorhofsreceptoren zum thorakalen Blutvolumen. Pflug.Arch.ges.Physiol. 271, 797-807.

Langston, J.B. & Guyton, A.C. (1958). Effect of epinephrine on the rate of urine formation. Amer.J.Physiol. 192, 131 - 134.

Larsell, O. (1921). Nerve terminations in the lung of the rabbit. J. comp.Neurol. 33, 105 - 131.

Larsell, O. (1922). The ganglia, plexuses, and nerve terminations of the mammalian lung and pleura pulmonalis. J. comp. Neurol. 35, 97 - 132.

Larsell, O. & Dow, R.S. (1933). The innervation of the human lung. Amer.J.Anat. 52, 125 - 146.

Lauson, H.D. & Bocanegra, M. (1961). Clearance of exogenous vasopressin from plasma in dogs. Amer.J.Physiol, 200, 493 - 497.

Lauson, H.D., Bradley, S.E. & Cournand, A. (1944). The renal circulation in shock. J. clin. Invest. 23, 381 - 402.

Ledsome, J.R., Linden, R.J., & O'Connor, W.J. (1961). The mechanisms by which distension of the left atrium produces diuresis in anaesthetized dogs. J.Physiol. 159, 87 - 100.

Lenfant, C., & Howell, B.J. (1960). Cardiovascular adjustments in dogs during continuous pressure breathing. J. appl. Physiol. 15, 425 - 428.

Levitt, M.F., Turner, L.B. & Sweet, A.Y. (1952). The effect of experimental venous obstruction on salt and water distribution and excretion in man. J.clin.Invest, 31, 885 - 894.

Lewis, A.A.G. (1953). The control of the renal excretion of water. Ann.R.Coll.Surg. Engl. 13, 36 - 54.

Linderholm, H. & Strandell, T. (1958). Heart volume in the prone and erect positions in certain heart cases. Acta.med.scand. 162, 247 - 261.

Lambardo, T.A., Eisenberg, S., Oliver, B.B., Viar, W.N., Eddleman, E.E., & Harrison, T.R. (1951). Effects of bleeding on electrolyte excretion and on glomerular filtration. Circulation 3, 260 - 270.

Loutit, J.F., Mollison, M.D. & van der Walt, E.D. (1942). Venous pressure during venesection and blood transfusion. Brit.med.J. 2, 658 - 661.

Love, A.H.G., Roddie, R.A., Rosenweig, I.J. & Shanks, R.G. (1957). The effect of pressure changes in the respired air on the renal excretion of water and electrolytes. Clin.Sci. 16, 281 - 296.

McDowall, R.J.S. (1938). 'The control of the circulation of the blood'. London: Longmans Green & Co.Ltd.

McLean, F.C. (1925). Edema as a problem in physiological regulation. Physiol Rev. 5, 618 - 640.

McMichael, J. (1937). Postural changes in cardiac output and respiration in man. Quart.J.exp.Physiol. 27, 55 - 72.

McMichael, J. (1944). Clinical aspects of shock. J.Amer.med.Ass. 124, 275 - 281.

McMichael, J. & Sharpey Schaefer, E.P. (1944). Cardiac output in man by a direct Fick method. Brit.Heart J. 6, 33 - 40.

MacWilliam, J.A. (1933). Postural effects on heart rate and blood pressure. Quart.J.exp.Physiol. 23, 1 - 33.

Mandel, E.E., Jones, F.L., Willis, M.J. & Cargill, W.H. (1953). Renal excretion of creatinine and inulin in man. J.Lab.clin.Med. 42, 621-637.

Marguth, H., Marguth, F. & Raule, W. (1951). Die pressorezeptoren der aorta unter pharmakologischer und mechanischer blutdruckerhohung. Arch.Int.Pharmacodyn. 87, 17 - 32.

Marshall, E.K.Jr., & Kolls,A.C. (1919). Studies on the nervous control of the kidney in relation to diuresis and urine secretion.

I. The effect of unilateral excision of the adrenal, section of the splanchnic nerve and section of the renal nerves on the secretion of the kidney.

II. A comparison of the changes caused by unilateral splanchnotomy with those caused by unilateral compression of the renal artery. Amer.J.Physiol. 49, 302 - 316, 317 - 325.

Marshall, R. & Widdicombe, J.G. (1958). The activity of pulmonary stretch receptors during congestion of the lungs. Quart.J.exp. Physiol, 43, 320 - 330.

Mattson, S.B. & Carlens, E. (1955). Lobar ventilation and oxygen uptake in man. Influence of body position. J. Thoracic Surg. 30, 676 - 682.

Mayerson, H.S. (1942). Effect of gravity on the blood pressure of the dog. Amer.J.Physiol. 135, 411 - 418.

Meek, W.J. & Eyster, J.A.E. (1921). Reactions to haemorrhage. Amer.J.Physiol. 56, 1 - 15.

Meek, W.J. & Eyster, J.A.E. (1922). The effect of plethora and variation in venous pressure on diastolic size and ouput of the heart. Amer.J.Physiol. 61, 186 - 202.

Merrill, J.P., Murray, J.E., Harrison, J.H. & Guild, W.R. (1956). Successful homotransplantation of the human kidney between identical twins. J.Amer.Med.Ass. 160, 277-282.

Meyling, H.A. (1953). Structure and significance of the peripheral extension of the autonomic nervous system. J. Comp. Neurol. 99, 495 - 543.

Mills, J.N. (1949). The influence upon the vital capacity of procedures calculated to alter the volume of blood in the lungs. J. Physiol. 110, 207 - 216.

Mitchell, C.A.G. (1956). Cardiovascular innervation. Edinburgh: Livingston.

Mueller, C.B., Surtshin, A., Carlin, M.R. & White, H.L. (1951). Glomerular and tubular influences on sodium and water excretion. Amer.J.Physiol. 165, 411 - 422.

Murdaugh, H.V.Jr., Sieker, H.O. & Manfredi, F. (1959). Effect of altered intrathoracic pressure on renal haemodynamics, electrolyte excretion and water clearance. J.clin.Invest. 38, 834 - 842.

Murphy, F.D., Correll, H. & Grill, J.C. (1941). The effects of intravenous solutions on patients with and without cardiovascular defects. J.Amer.Med.Ass. 116, 104 - 108.

Neil, E. (1954). The carotid and aortic vasosensory areas. Their contribution to circulatory and respiratory adjustments occurring after haemorrhage. Arch.Middlesex Hosp. 4, 16 - 27.

Neil, E. (1960). Afferent impulse activity in cardiovascular receptor fibres. Physiol. Rev. 40, Suppl.4, 201 - 208.

Nelson, J.R. & Smith, J.R. (1959). The pathologic physiology of pulmonary embolism. A physiologic discussion of the vascular reactions following pulmonary arterial obstruction by emboli of varying size. Amer.Heart J. 58, 916 - 932.

Netravisesh, V. (1953). Effects of posture and of neck compression on outputs of water, sodium and creatinine. J.appl.Physiol, 5, 544 - 548.

Nettleship, W.A. (1936). Experimental studies on the afferent innervation of the cat's heart. J.comp.Neurol. 64, 115 - 133.

Noble, R.L. & Taylor, N.B.G. (1953). Antidiuretic substances in human urine after haemorrhage, fainting, dehydration and acceleration. J.Physiol. 122, 220 - 237.

Nonidez, J.F. (1935). The aortic (depressor) nerve and its associated epithelioid body, the glomus aorticum. Amer. J. Anat. 57, 259 - 301.

Nonidez, J.F. (1937). Identification of the receptor areas in the venae cavae and pulmonary veins which initiate reflex cardiac acceleration. (Bainbridge's reflex). Amer. J. Anat. 61, 203 - 223.

Nonidez, J.F. (1939). Studies on the innervation of the heart. I. Distribution of the cardiac nerves, with special reference to the identification of the sympathetic and parasympathetic postganglionics. Amer.J.Anat. 65, 361-401.

Nonidez, J.F. (1941). Studies on the innervation of the heart. II. Afferent nerve endings in the large arteries and veins. Amer.J.Anat. 68, 151 - 178.

Nonidez, J.F. (1943). The structure and innervation of the conductive system of the heart of the dog and rhesus monkey as seen with a silver impregnation technique. Amer. Heart J. 26, 577 - 597.

O'Connor, W.J. (1946). The effect of section of the supraoptico-hypophyseal tracts on the inhibition of water-diuresis by emotional stress. Quart.J.exp.Physiol. 33, 149-161.

O'Connor, W.J. (1955). The excretion of administered sodium chloride by the conscious dog, and the effect of occlusion of the carotid arteries. Quart.J.exp.Physiol. 40, 237-257.

O'Connor, W.J. (1958a). The effect on the urinary volume and composition of the ingestion of 0.9% sodium chloride and of occlusion of the carotid arteries. Quart.J.exp.Physiol. 43, 367 - 383.

O'Connor, W.J. (1958b). The effect on the volume and composition of the urine of the infusion of adrenaline and noradrenaline. Quart.J.exp.Physiol. 43, 384 - 393.

O'Connor, W.J. (1962). Renal Function. London: Edward Arnold.

O'Connor, W.J. & Verney, E.B. (1942). The effect of removal of the posterior lobe of the pituitary and the inhibition of water diuresis by emotional stress. Quart.J.exp.Physiol. 31, 393 - 408.

O'Connor, W.J. & Verney, E.B. (1945). The effect of increased activity of the sympathetic system in the inhibition of water diuresis by emotional stress. Quart.J.exp.Physiol. 33, 77 - 90.

O'leary, J., Heinbecker, P. & Bishop, G.H. (1934). The fiber constitution of the depressor nerve of the rabbit. Amer.J.Physiol. 109, 274 - 285.

Opdyke, D.F., Van Noate, H.F. & Brecher, G.A. (1950). Further evidence that inspiration increases right atrial inflow. Amer.J.Physiol, 162, 259 - 265.

Paintal, A.S. (1953a). A study of right and left atrial receptors. J.Physiol. 120, 596 - 610.

Paintal, A.S. (1953b). The conduction velocities of respiratory and cardiac afferent fibres in the vagus nerves. J. Physiol. 121, 341 - 359.

Paintal, A.S. (1955). A study of ventricular pressure receptors and their role in the Bezold Reflex. Quart.J.exp.Physiol. 40, 348 - 363.

Pannier, R. (1940). Contribution a l'etude de l'innervation presso-et chemo-sensible des oreillettes et des vaisseaux de la base du coeur. Arch.int.Pharmacodyn. 64, 476 - 484.

Pappenheimer, J.R. (1960). Central control of renal circulation. Physiol.Rev= suppl.4. 40, 35 - 37.

Papper, S., Saxon, L., Burg, M.B., Siefer, H.W. & Rosenbaum, J.D. (1957). The effect of morphine sulphate upon the renal excretion of water and solute in man. J.Lab.clin.Med. 50, 692 - 704.

Partridge, R.C. (1933). Afferent impulses in the vagus nerve. J.cell.comp.Physiol. 2, 367 - 380.

Partridge, R.C. (1939). Respiratory accelerator action of the carotid sinus-cardiac depressor mechanism. J.Physiol. 96, 233 - 239.

Pearce, J.W. (1959). The effect of vagotomy and denervation of the carotid sinus on diuresis following plasma volume expansion. Can. J. Biochem. Physiol. 37, 81 - 90.

Pearce, J.W. (1961). A current concept of the regulation of blood volume. Brit. Heart J. 23, 66 - 74.

Pearce, J.W. & Henry, J.P. (1955). Changes in cardiac afferent nerve fibre discharges resulting from haemorrhage and adrenaline. Amer. J. Physiol. 183, 650.

Pearce, J.W. & Whitteridge, D. (1951). The relation of pulmonary arterial pressure variations to the activity of afferent pulmonary vascular fibres. Quart.J.exp.Physiol. 36, 177 - 188.

Pearce, M.L. & Newman, E.V. (1954). Some postural adjustments of salt and water excretion. J.clin.Invest. 33, 1089-1094

Perlmutt, J.H. (1961). Renal activity of vasopressin in anaesthetized dogs. Amer.J.Physiol. 200, 400 - 404

Peters, J.P. (1935). Body water: the exchange of fluids in man' Springfield, Illinois. Charles C. Thomas.

Petersdorf, R.G. & Welt, L.G. (1953). The effect of an infusion of hyperoncotic albumin on the excretion of water and solutes. J.clin.Invest. 32, 283 - 291.

Pickford, M. (1945). Control of the secretion of the antidiuretic hormone from the pars nervosa of the pituitary gland. Physiol. Rev. 25, 573 - 595.

Pickford, M. (1952). Antidiuretic substances. Pharmacol.Rev. 4, 254 - 258.

Pickford, M. & Watt, J.A. (1951). Comparison of some of the actions of adrenaline and noradrenaline on the kidney. Quart.J. exp. Physiol. 36, 205 - 212.

Pitts, R.F. & Duggan, J.J. (1950). Studies on diuretics. II. The relationship between glomerular filtration rate, proximal tubular absorbtion of sodium and diuretic efficacy of mercurials. J.clin.Invest. 29, 372 - 379.

Popenoe, E.A., Lawler, H.C. & du Vigneaud, V. (1952). Partial purification and amino acid content of vasopressin from hog posterior pituitary glands. J.Amer.chem.Soc. 74, 3713.

Price, H.L., Conner, E.H., Elder, J.D. & Dripps, R.D. (1952). Effect of sodium thiopental on circulatory response to positive pressure inflation of lung. J.appl.Physiol. 4, 629 - 635.

Price, H.L., King, B.D., Elder, J.D., Libien, B.H. & Dripps, R.D. (1951). Circulatory effects of raised airway pressure during cyclopropane anaesthesia in man. J.clin. Invest, 30, 1243 - 1249.

Priestley, J.G. (1916). The regulation of excretion of water by the kidneys. II. J.physiol. 50, 304 - 311.

Rahn, H., Otis, A.B., Chadwick, L.E. & Fenn, W.O. (1946). The pressure-volume diagram of the thorax and lung. Amer.J.Physiol. 146, 161 - 178.

Raisz, L.G., Anslow, W.P.jr. & Wesson, L.G.jr. (1950). Cardiovascular changes induced by rapid expansion of the extracellular fluid. Pro.Soc.exp.Biol., N.Y. 74, 401 - 403.

Ralston, L.A., Cobb, L.A. & Bruce, R.A.(1961). Acute circulatory effects of arterial bleeding as determined by indicator dilution curves in normal human subjects. Amer.Heart J. 61, 770-776.

Reeves, J.L., Henry, J.P. & Gauer, O.H. (1956). Three methods of inducing graded obstruction of the pulmonary circulation. Amer.J.vet.Res. 17, 98 - 102.

Remington, J.W. & Baker, C.H. (1959). Plasma volume changes accompanying reactions to infusions of blood or plasma. Amer. J. Physiol. 197, 193 - 200.

Rijlant, P. (1932). Le courant d'action du nerf depresseur. C.R.Soc.Biol. Paris. 110, 589 - 591.

Riley, R.L., Permutt, S., Said, S., Godfrey, M., Cheng, T.O., Howell, J.B.L. & Shepard, R.H. (1959). Effect of posture on pulmonary dead space in man. J.appl.Physiol.14, 339-344.

Ritter, E.R. (1952). Pressure/flow relations in the kidney. Alleged effects of pulse pressure. Amer.J.Physiol. 168, 480 - 489.

Root, W.S., Allison, J.B., Cole, W.H., Holmes, J.H., Walcott, W.W. & Gregersen, M.I. (1947). Disturbances in the chemistry and in the acid-base balance of the blood of dogs in haemorrhagic and traumatic shock. Amer.J.Physiol. 149, 52 - 63.

Root, W.S., Walcott, W.W. & Gregerson, M.I. (1947). Effects of muscle trauma and of haemorrhage upon the cardiac ouput of the dog. Amer.J.Physiol. 151, 34 - 44.

Ruch, T.C. & Fulton, J.F. (1960). 'Medical physiology and Biophysics'. London: W.B.Saunders & Co.

Rydin, H. & Verney, E.B. (1937). The inhibition of water diuresis by emotional stress and by muscular exercise. Quart.J.exp. Phys. 27, 344 - 374.

Sato, H. (1954). Innervation of heart in dog. Tohoku J.exp.Med. 59, 343 - 356.

Selkurt, E.E. (1946). Renal blood flow and renal clearance during haemorrhagic shock. Amer.J.Physiol. 145, 699 - 709.

Selkurt, E.E. (1954). Sodium excretion by the mammalian kidney. Physiol. Rev. 34, 287 - 333.

Selkurt, E.E., Hall, P.W. & Spencer, M.P. (1949). Influence of graded arterial pressure decrement on renal clearance of creatinine, p-aminohippurate and sodium. Amer.J.Physiol. 159, 369 - 378.

Shannon, J.A. (1942a). The control of the renal excretion of water. I.The effect of variations in the state of hydration on water excretion in dogs with diabetes insipidus. J.exp. Med. 76, 371 - 386.

Shannon, J.A. (1942b). The control of the renal excretion of water. II. The rate of liberation of the posterior pituitary antidiuretic hormone in the dog. J.exp.Med. 76, 387 - 399.

Sharpey-Schafer, E.P. & Bain, W.A. (1932). The effects of changes in intrapulmonary air pressure on the pulmonary and aortic circulation of the dog. Quart.J.exp.Physiol. 22, 101 - 147.

Sharpey-Schafer, E.P. & Wallace, J. (1942). Circulatory overloading following rapid intravenous injections. Brit.Med.J. 2. 304 - 308.

Sieker, H.O., Gauer, O.H. & Henry, J.P. (1954). The effect of continuous negative pressure breathing on water and electrolyte excretion by the human kidney. J.clin.Invest. 33, 572 - 577.

Sjostrand, T. (1952). The regulation of blood distribution in man. Acta. physiol scand. 26, 312 - 327.

Sjostrand, T. (1953). Volume and distribution of blood and their significance in regulating circulation. Physiol.Rev. 33. 202 - 228.

Smirnow, A. (1895). Ueber die sensiblen Nervendigungen im Herzen bei Amphibien und Saugetieren. Anat.Anz.10, 737 - 749.

Smith, H.W. (1951). 'The Kidney. Structure and function in health and disease'. New York: Oxford University Press.

Smith, H.W. (1957). Salt and water volume receptors. An exercise in physiologic apologetics. Amer.J.Med. 23, 623 - 652.

Smythe, C.McC., Nickel, J.F. & Bradley, S.E. (1952). The effect of epinephrine (USP), l-epinephrine, and l-norepinephrine on glomerular filtration rate, renal plasma flow, and the urinary excretion of sodium, potassium, and water in normal man. J.clin.Invest. 31, 499 - 506.

Sobel, S., Marotta, S.F. & Marbarger, J.P. (1959). Circulating plasma volume changes in anaesthetized dogs during positive pressure breathing. J.appl.Physiol.14, 937-939.

Starling, E.H. (1899). The glomerular functions of the kidney. J.Physiol. 24, 317 - 330.

Starling, E.H. (1909). 'The Fluids of the Body'. The Mercers' Company Lectures. London: Archibald Constable & Co.Ltd. p.134.

Starling, E.H. & Verney, E.B. (1925). The secretion of urine as studied on the isolated kidney. Proc.Roy.Soc. B.97, 321 - 363.

Steinberg, B. & Mundy, C.S. (1936). Experimental pulmonary embolism and infarction. Arch.Path. 22, 529 - 542.

Strauss, M.B. (1957). 'Body water in man'. London: Churchill.

Strauss, M.B., Davis, R.K., Rosenbaum, J.D. & Rossmeisl, E.C.(1951). "Water Diuresis" produced during recumbency by the intravenous infusion of isotonic saline solution. J.clin.Invest. 30, 862 - 868.

Surtshin, A. & Hoeltzenbein, J. (1954). Excretion of sodium and water by the denervated canine kidney. Amer.J.Physiol. 177, 44 - 48.

Surtshin, A., Hoeltzenbein, J. & White, H.L. (1955). Some effects of negative pressure breathing on urine excretion. Amer.J.Physiol. 180, 612-616.

Surtshin, A., Mueller, C.B. & White, H.L. (1952). Effect of acute changes in glomerular filtration rate on water and electrolyte excretion: mechanism of denervation diuresis. Amer. J. Physiol. 169, 159 - 173.

Surtshin, A. & White, H.L. (1956). Postural effects on renal tubular activity. J.clin.Invest. 35, 267 - 271.

Swan, A.A.B. & Whitteridge, D. (1956). Baroreceptor fibres from the pulmonary artery. Abst.XXint.physiol Cong. 867-868.

Takino, M. (1933). Vergleichende Studien uber die histologische Struktur der Arteriae und Venae pulmonales, die Blutgefassnerven der Lunge und die Nerven der Bronchien bei verschiedenen tierarten, besonders uber die Beziehung der Blutgefassnerven zu den glatten Muskeln der Blutgefasse. III. Mitteilung. Acta.Sch.med.Univ.Kioto, 15, 321 - 354.

Takino, M. & Watanabe, S. (1937). Uber die Bedeutung de Ligamentum arteriosum BZW. des Ductus Botalli und der Ansatzselle desselben an der Pulmonalwand (A. pulm.) als Blutdruckzugler bei verschiedenen Tierarten. Arch. Kreislaufforsch. 11, 18 - 27.

Tcheng, K.T. (1951). Innervation of the dog's heart. Amer.Heart J. 41, 512 - 524.

Tello, J.F. (1924). Development et Terminaison du nerf depresseur. J.Trab.Lab.Invest.Biol. Univ.Madrid. 22, 295 - 308

Tenney, S.M. (1959). Fluid volume redistribution and thoracic volume changes during recumbency. J.appl.Physiol. 14, 129 - 132.

Theobald, G.W. (1934). The repetition of certain experiments on which Molitor and Pick base their water-centre hypothesis, and the effect of afferent nerve stimuli on water diuresis. J. Physiol. 81, 243 - 254.

Thomas, S. (1957). Some effects of change of posture on water and electrolyte excretion by the human kidney. J.Physiol. 139, 337 - 352.

Thomson, D.D., Barrett, M.J. & Pitts, R.F. (1951). Significance of glomerular perfusion in relation to variability of filtration rate. Amer.J.Physiol. 167, 546 - 552.

Thompson, W.O., Thompson, P.K. & Dailey, M.E. (1928). The effect of posture upon the composition and volume of the blood in man. J.clin .Invest. 5, 573 - 604.

Thorn, N.A. (1958). Mammalian Antidiuretic Hormone. Physiol.rev. 38, 169 - 195.

Ting, E.Y., Hong, S.K. & Rahn, H. (1960). Cardiovascular responses of man during negative pressure breathing. J. appl. Physiol. 15, 557 - 560.

Ullmann, E. (1961). Acute anoxia and the excretion of water and electrolyte. J. Physiol. 155, 417 - 437.

Valtin, H., Wilson, I.D. & Tenney, S.M. (1959). CO_2 diuresis, with special reference to the role of the left atrial stretch receptor mechanism. J.Appl.Physiol. 14, 844-848.

Verney, E.B. (1926). The secretion of pituitrin in mammals as shown by perfusion of the isolated kidney of the dog. Proc.Roy.Soc.B. 99, 487 - 517.

Verney, E.B. (1929). Goulstonian Lectures on Polyuria. I. Polyuria associated with pituitary dysfunction. Lancet, 216, 539 - 546.

Verney, E.B. (1947). The antidiuretic hormone and the factors which determine its release. Proc.Roy.Soc. B, 135, 25 - 106.

Verney, E.B. (1954). Water diuresis. Irish J.med.Sci. 6th Series, 345, 377 - 402.

Walsh, E.G. (1947). Vagal nerve fibre activity following multiple pulmonary embolism. J.Physiol, 106, 466-470.

Walsh, E.C. & Whitteridge, D. (1944). Vagal activity and the tachypnoea produced by multiple pulmonary emboli. J.Physiol. 103, 37P.

Walton, R.P., Richardson, J.A., Walton, R.P.jr. & Thompson, W.L. (1959). Sympathetic influences during haemorrhagic hypotension. Amer. J. Physiol. 197, 223 - 230.

Warren, J.V., Brannon, E.S., Stead, E.A. Jr. & Merrill, A.J.(1945). The effect of venesection and the pooling of blood in the extremities on the atrial pressure and cardiac output in normal subjects with observations on acute circulatory collapse in three instances. J.clin.Invest, 24, 337 - 344.

Warren, J.V., Brannon, E.S., Weens, H.S. & Stead, E.A.jr. (1948). Effect of increasing the blood volume and right atrial pressure on the circulation of normal subjects by intravenous infusions. Amer.J.Med, 4, 193 - 200.

Warren, J.V., Stead, E.A.jr., (1943). The effect of the accumulation of blood in the extremities on the venous pressure of normal subjects. Amer.J.med.Sci. 205, 501 - 505.

Warthen, H.J. (1935). Massive intravenous injections. Arch.Surg., Chicago, 30, 199 - 227.

Waterfield, R.L. (1931). The effects of posture on the circulating blood volume. J.Physiol. 72, 110 - 120.

Watts, D.T. (1956). Arterial blood epinephrine levels during haemorrhagic hypotension in dogs. Amer.J.Physiol, 184, 271 - 274.

Weinstein, H., Berne, R.M. & Sachs, H. (1960). Vasopressin in blood: effect of haemorrhage. Endocrinology, 66, 712-718.

Welt, L.G. (1960). Volume receptors. Circulation, 21, 1002-1008.

Welt, L.G. & Orloff, J. (1951). The effects ofan increase in plasma volume on the metabolism and excretion of water and electrolytes by normal subjects. J.clin.Invest. 30, 751 - 761.

Werko, L. (1947). The influence of positive pressure breathing on the circulation in man. Acta.med.scand. Suppl.193, 1-125.

Wesson, L.G. jr. (1957). Glomerular and tubular factors in the renal excretion of sodium chloride. Medicine, 36, 281 - 396.

Whitteridge, D. (1948). Afferent nerve fibres from the heart and lungs in the cervical vagus. J.Physiol. 107, 496-512.

Whitteridge, D. (1950). Multiple embolism of the lung and rapid shallow breathing. Physiol.Rev. 30, 475 - 486.

Whitteridge, D. (1952). Afferent paths of cardiovascular reflexes. In 'Visceral Circulation' Ed. G.E.W.Wolstenholme. Ciba Foundation Symposium. London: Churchill.

Whitteridge, D. (1955). Reflexes arising from the great veins and the pulmonary circulation. Brit.J.Anaesth. 27, 274 - 275.

Widdicombe, J.G. (1954a). Receptors in the trachea and bronchi of the cat. J.Physiol. 123, 71 - 104.

Widdicombe, J.G. (1954b). The site of pulmonary stretch receptors in the cat. J.Physiol. 125, 336 - 351.

Wiggers, C.J. (1949). 'Physiology in Health and Disease'. 5th Ed. London: Henry Kimpton.

Wiggers, C.J. (1952). 'Circulatory Dynamics'. New York: Grune & Stratton.

Wiggins, W.S., Manry, C.H., Lyons, R.H. & Pitts, R.F. (1951). The effect of salt loading and salt depletion on renal function and electrolyte excretion in Man. Circulation, 3, 275 - 281.

Wilkins, R.W., Tinsley, C.M., Culbertson, J.W., Burrows, B.A., Judson, W.E. & Burnett, C.H. (1953). Effects of venous congestion

of the limbs upon renal clearances and the excretion of water and salt. I. Studies in normal subjects and in hypertensive patients before and after splanchnicectomy. J. clin. Invest. 32, 1101 - 1116.

Witham, A.C., Fleming, J.W. & Bloom, W.L. (1951). The effect of the intravenous administration of dextran on cardiac output and other circulatory dynamics. J.clin. Invest. 30, 897 - 902.

Woollard, H.H. (1926). The innervation of the heart. J. Anat. London. 60, 345 - 373.

Yeomans., A, Porter, R.R. & Swank, R.L. (1943). Observations on certain manifestations of circulatory congestion produced in dogs by rapid infusion. J.clin.Invest. 22, 33 - 45.

Young, I.E., Pearce, J.W. & Stevenson, J.A.F. (1955). Renal responses to hypervolaemia in the dog. Can.J.Biochem. Physiol. 33, 800 - 810.

Zuidema, G.D., Clarke, N.P., Reeves, J.L., Gauer, O.H. & Henry, J.P. (1956). Influence of moderate changes in blood volume on urine flow. Amer. J. Physiol. 186, 89 - 91.